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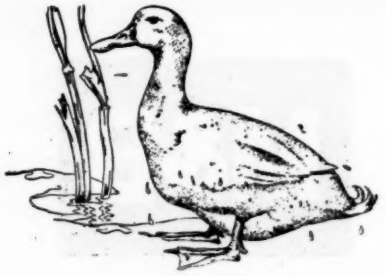

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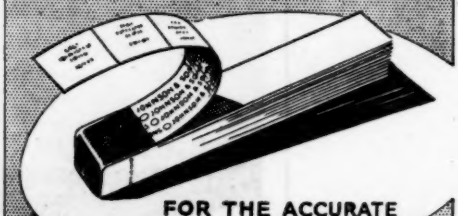

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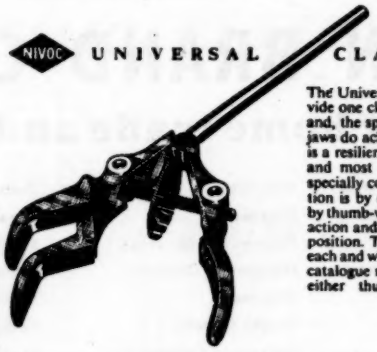

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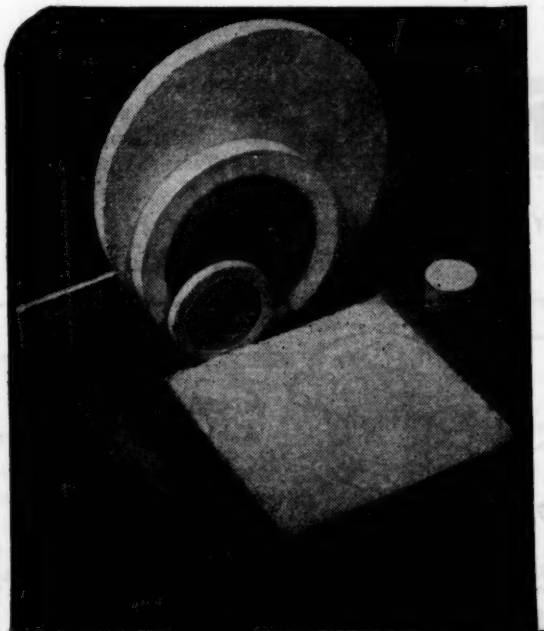

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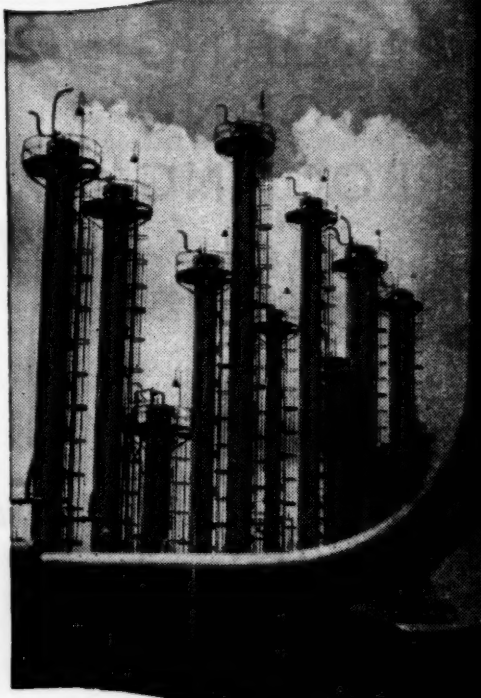

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413. *Configuration of the* cyclo*Hexan-2-ol-1-carboxylic Acids and their Derivatives.*

By José Pascual, José Sistaré, and Antonio Regás.

The configuration of the two *cyclo*hexan-2-ol-1-carboxylic acids has been established (*cis*, m. p. 80—81°; *trans*, m. p. 111°) by chemical reactions and physical properties, and various known and new derivatives have been stereochemically related to the acids. Differences in reactivity have been observed for each pair of isomerides, the *cis*-forms being always the more reactive. In almost all such instances the *cis*-compound can form an intramolecular hydrogen bridge.

A *cyclo*hexan-2-ol-1-carboxylic acid, m. p. 111°, was obtained simultaneously by Einhorn and Meyerberg (*Ber.*, 1894, **27**, 2472), who treated 2-amino*cyclo*hexane-1-carboxylic acid with nitrous acid, and by Dieckmann (*ibid.*, p. 2476), who reduced ethyl *cyclo*hexan-2-one-1-carboxylate with sodium amalgam, and later by Gardner, Perkin, and Watson (*J.*, 1910, **97**, 1764), who reduced *cyclo*hexan-2-one-1-carboxylic acid also with sodium amalgam. Still later, catalytic hydrogenation of salicylic acid and its esters was repeatedly used (Houben and Pfau, *Ber.*, 1916, **49**, 2295; Díaz Aguirreche, *Anal. Fís. Quím.*, 1927, **25**, 313; I.G. Farbenind. A.-G., B.P. 286,201; Connor and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 4678; Edson, *J. Soc. Chem. Ind.*, 1934, **53**, 138T; Packendorff, *Ber.*, 1935, **66**, 1251; Mitsui, *Mem. Coll. Sci. Kyoto Imp. Univ.*, 1935, *A*, 329) to prepare the corresponding hexahydro-derivatives, but was often complicated by hydrogenolysis of the hydroxyl and even of the carboxyl group.

Special mention should be made of the work of Balaš and Šrol (*Coll. Trav. chim. Czech.*, 1929, **1**, 658), who hydrogenated *o*-, *m*-, and *p*-hydroxybenzoic acid in presence of platinum black, obtaining the hexahydro-derivatives in two geometrically isomeric forms in each case. Salicylic acid yielded the *cyclo*hexan-2-ol-1-carboxylic acid, m. p. 111°, mentioned above, and a small proportion of an isomeride, m. p. 70—71°. Boeseken and his collaborators (*Rec. Trav. chim.*, 1933, **52**, 881) obtained the second isomeride in a still less pure form (m. p. 57—63°). Then Marshall, Kuck, and Elderfield (*J. Org. Chem.*, 1942, **7**, 454) isolated the second acid as the main product of high-pressure hydrogenation and subsequent hydrolysis of methyl salicylate, and gave its melting point as 76—78°. The same product resulted predominantly when ethyl *cyclo*hexan-2-one-1-carboxylate was hydrogenated in presence of platinum oxide and then hydrolysed (Pascual and Sistaré, *Anal. Fís. Quím.*, 1946, **42**, 667), and we now find its melting point to be somewhat higher (80—81°) than that given by the American authors.

Balaš and Šrol believed that the 111° acid was the *cis*-form, as for *cyclo*hexan-3- and -4-ol-1-carboxylic acid the *cis*- were the higher-melting forms. On the other hand, Boeseken *et al.* (*loc. cit.*) ascribed the *cis*-configuration to the lower-melting isomeride, as it alone increased the conductivity of boric acid.

We believe that the 81° acid is the *cis*-, and the 111° acid is the *trans*-form, for the following reasons.

(1) Reduction of ethyl *cyclo*hexan-2-one-1-carboxylate in a neutral medium (with sodium amalgam; Dieckmann) yields mostly the 111° acid, whereas reduction with platinum oxide gives almost wholly the ethyl ester of the 81° acid. The general rule, similar to Skita's, connecting these conditions with configuration has been repeatedly stated by Vavon and Godchot (cf. Godchot, *Bull. Soc. chim.*, 1934, [v], **1**, 1186). That reduction of ethyl *cyclo*hexan-2-one-1-carboxylate in presence of platinum oxide yields almost exclusively the ester of the 81° acid follows because hydrolysis of the product gives the latter acid directly in spite of its higher solubility.

(2) The same conclusion is reached by comparing the viscosities of the ethyl esters; Pascual and Sistaré (*loc. cit.*) obtained for those viscosities a ratio similar to that which has now been found for the methyl esters. The physical constants of the two pure methyl esters, which we prepared from the pure acids by diazomethane, support these configurations. In accordance with von Auwers and Skita's rule, the methyl ester of the 81° acid has the higher density, higher refractive index, and lower molecular refractivity. The relative viscosities are still more decisive. According to Thole (cf. Gough, Huntress, and Kenyon, *J.*, 1926, 2052), when groups in the 1 : 2-positions have a large residual affinity for each other, proximity of the groups can cause intramolecular neutralisation of affinities (in the present case probably with formation of a hydrogen bridge between the carbonyl oxygen of the acid group and the hydrogen of the hydroxyl group), so that the *cis*-compound, being less associated, has the lower viscosity; for the methyl esters now under consideration the viscosity of the 81° derivative is approximately

half of that of the 111° derivative. The boiling points of the methyl esters also accord with the configurations assigned; according to Hunter (*Ann. Reports*, 1946, **43**, 144), " in the case of isomeric compounds, that isomer which can achieve intramolecular hydrogen-bond structure is markedly more volatile than that which cannot."

Besides some liquid esters, which are probably mixtures of isomerides, the following derivatives of the *cyclo*hexan-2-ol-1-carboxylic acids are recorded (*cis* and *trans* refer to the 81° and 111° acid, respectively).

Derivatives of known configuration: ethyl *cis*-2-nitrobenzoyloxy*cyclo*hexane-1-carboxylate, m. p. 71—72° (Pascual and Sistaré, *loc. cit.*); ethyl *trans-cyclo*hexan-2-ol-1-carboxylate (obtained from the *trans*-acid by alcohol and sulphuric acid), b. p. 120—121°/30 mm. (Einhorn and Meyerberg, *loc. cit.*), 130—132°/25 mm. (Pascual and Sistaré).

Derivatives of unknown configuration: an amide, m. p. 113·7—114·7° (Marshall *et al.*, *loc. cit.*); two acetyl derivatives, m. p. 96—101° (Eason and Pyman, *J. Soc. Chem. Ind.*, 1933, **52**, 97T) and 66·1—66·7° (Marshall *et al.*), respectively; two *p*-toluidide acetates, m. p. 154·5—155·9° and 124—143°, respectively (Marshall *et al.*).

Our work has established the configuration of some of these compounds and added a few more, as shown in the following table:

	Melting points.	
	cis.	*trans*.
(i) *cyclo*Hexan-2-ol-1-carboxylic acid	81°	111°
(ii) 2-Acetoxy-acid, from (i)	65·5—66·5 *	104·5—105·3 *
(iii) 2-Acetoxy-*p*-toluidide, from (ii)	155—156 *	154·5—155·5 *
(iv) p-*Toluidide* of (i), from (i), (iii), or (v)...	190·6—191·4 *	178·3—178·9 *
(v) *Methyl* ester, from (i)	(b. p. 105°/14 mm.)	(b. p. 115°/14 mm.)
(vi) Amide of (i), from (v)	113—115	—

* Corr.

The relations of these substances to those described in the literature will be apparent.

The differing reactivity of the hydroxyl and carboxyl groups, observed in several of the pairs of compounds under consideration, must be related to the configuration. Thus, the *cis*-acid gives the acetyl derivative when boiled with acetyl chloride in ether, whereas the *trans*-form requires the presence of pyridine; similarly, Pascual and Sistaré (*loc. cit.*) obtained a *p*-nitrobenzoyl derivative of the *cis*- but not of the *trans*-ethyl ester. In reactions affecting the carboxyl and carbomethoxy-group, when the hydroxyl group is free, the *cis*-derivative is also the more reactive: the *cis*-acid and its methyl ester yield a *p*-toluidide when boiled with *p*-toluidine, whereas the *trans*-compounds react with difficulty; the *trans*-amide could not be obtained from the ester; and hydrolysis of the acetylated *p*-toluidide is much easier in the *cis*- than in the *trans*-series.

These differing reactivities are caused by the ability of the *cis*-forms to form internal hydrogen bridges. Intermolecular association of the *trans*-forms is shown in, *e.g.*, the higher viscosity of its methyl ester. Further work is in hand to decide whether the differences, *e.g.*, in the formation of amides, persist when the hydroxyl groups are methylated.

Experimental.

Ethyl cyclo*Hexan-2-one-1-carboxylate.*—This was prepared by the method of *Org. Synth.*, Coll. Vol. II, 531, or of Pascual and Sistaré (*loc. cit.*).

Hydrogenation of Ethyl cyclo*Hexan-2-one-1-carboxylate. Preparation of* cis- *and* trans-cyclo*Hexan-2-ol-1-carboxylic Acid.*—An apparatus similar to that described by Adams and Voorhees (*Org. Synth.*, Coll. Vol. I, 2nd. Edn., p. 61) was used. Ethyl *cyclo*hexanonecarboxylate (150 g.) was hydrogenated in its own volume of absolute alcohol containing platinic oxide (2·2 g.) at room temperature and 5 atmospheres; after 20 hours' stirring the pressure had dropped to 2 atmospheres and then remained constant. After filtration and removal of the solvent, the product was distilled through a Vigreux column, to give methyl *cyclo*hexanolcarboxylate (120 g.), b. p. 117—118°/17 mm. This ester was mixed with hot 25% sodium hydroxide solution (400 ml.), stirred while cooling, and set aside at room temperature; next day, the sodium salt (120 g.) which had separated was filtered off, washed with a little alcohol, and dried. This salt was dissolved in the smallest possible amount of water and decomposed by 10% hydrochloric acid, and the solution saturated with amonium sulphate and extracted with ether. The ethereal layer was dried and, on evaporation in a vacuum, gave the acid (80 g.), m. p. 78°, which after crystallisation from ether had m. p. 80—81° (corr.).

The *cis*-acid remaining in solution, probably with some of the *trans*-form, was recovered as the latter after boiling it with alkali which set up an equilibrium (see below).

The mother-liquors from the sodium salt were mixed with the alcoholic washings, the alcohol was removed, more alkali added, and the whole boiled for 30 hours. The cold solution was made acid to Congo-red, saturated with ammonium sulphate, and extracted with ether. The ethereal solution was dried and the solvent distilled off, giving 10 g. of an acid, m. p. 106—110°.

The total yield of the two acids was 90%, the ratio of *cis*- and *trans*-forms being 8 : 1.

Transformation of the cis- *into the* trans-*Acid by boiling it in Alkaline Solution.*—The acid, m. p. 78° (15 g.), was heated under reflux in 7·5N-potassium hydroxide (150 ml.) for *ca.* 35 hours. The cold liquid was made acid to Congo-red, saturated with ammonium sulphate, and extracted with ether. 9·8 G. of an acid, m. p. 102°, were obtained which, when recrystallised from ethyl acetate, had m. p. 110—111°.

Methyl cis-cyclo*Hexan*-2-*ol*-1-*carboxylate.*—The *cis*-acid (10 g., 0·069 mol.) in absolute ether (*ca.* 55 ml.) was treated in the cold with a 2·95% solution (100 ml., 0·07 mol.) of diazomethane in ether. The resulting solution was treated as usual, and the extract was distilled in a vacuum, to give the *methyl* ester, b. p. 105°/14 mm., d_{25}^{25} 1·0989, n_D^{25} 1·4645, η^{25} 9·50 (yield, almost quantitative) (Found : C, 61·1; H, 8·7. $C_8H_{14}O_3$ requires C, 60·8; H, 8·9%).

cis-cyclo*Hexan*-2-*ol*-1-*carboxyamide.*—An alcoholic solution of the methyl ester, saturated with dry ammonia, was heated in a sealed tube at 100° for 12 hours, the alcohol distilled off, and the residue treated with absolute ether. In a short while, the amide crystallised; m. p. 113—115°.

cis-cyclo*Hexan*-2-*ol*-1-*carboxy*-p-*toluidide.*—(a) *From the acid.* 1 G. of acid was heated under reflux with 2 g. of *p*-toluidine at 150° for 2 hours; the resulting product, when cold, was treated with an excess of 25% sulphuric acid, and the residue filtered off, washed several times with a little water, and dried. The p-*toluidide* (1 g.), recrystallised twice from methanol, melted at 190·6—191·4° (corr.).

(b) *From the methyl ester.* The methyl ester (1 g.) and *p*-toluidine (2 g.) were heated for approx. 3 hours at 150°. The product, when cold, was treated as above, the same *p*-toluidide being obtained (Found : N, 6·2. $C_{14}H_{19}O_2N$ requires N, 6·0%).

cis-2-*Acetoxy*cyclo*hexanecarboxylic Acid.*—A procedure similar to that of Marshall *et al.* (*loc. cit.*) was used. The acid, m. p. 80° (1 g.), ether (25 ml.), and acetyl chloride (10 g.) were heated under reflux for 4 hours. The ether and excess of acetyl chloride were removed by distillation, first at atmospheric pressure and then in a vacuum, giving an oil which did not crystallise. When distilled at 175—180°/15 mm., it crystallised in a few hours. The product was recrystallised from ether–light petroleum, forming prisms, m. p. 65·5—66·5° (corr.).

cis-2-*Acetoxy*cyclo*hexane*-1-*carboxy*-p-*toluidide.*—The above acetyl derivative (0·5 g.) was heated under reflux with thionyl chloride (2—3 ml.) for 1 hour. The excess of chloride was then distilled off, finally in a vacuum. The residue was dissolved in a little absolute ether and poured on a solution of *p*-toluidine (1 g.) in ether (a few ml.), with cooling, and set aside for a few hours. The ethereal solution was shaken twice with 2N-sulphuric acid, twice with water, and then dried. Removal of the solvent gave a crystalline residue which, recrystallised from ether–light petroleum, had m. p. 155—156° (corr.).

This *p*-toluidide acetate (0·1 g.) was kept for a few hours in 0·5N-methanolic potassium hydroxide (5 ml.). The insoluble material was then filtered off, washed several times with water, and dried. It was identified as *cis-cyclo*hexan-2-ol-1-carboxy-*p*-toluidide by its m. p. (190—191·5°) and mixed m. p.

Methyl trans-cyclo*Hexan*-2-*ol*-1-*carboxylate.*—This *ester*, prepared from the *trans*-acid by the method used for the *cis*-isomeride, had b. p. 115°/14 mm., m. p. 35—36° (corr.), d_{25}^{25} (supercooled) 1·0899, n_D^{25} 1·4640, η^{25} 18·5 (Found : C, 60·8; H, 8·6. $C_8H_{14}O_3$ requires C, 60·8; H, 8·9%).

trans-cyclo*Hexan*-2-*ol*-1-*carboxy*-p-*toluidide.*—(a) *From the acid.* Prepared in the same way as was its *cis*-isomeride, but with heating at 160° for 3 hours, the p-*toluidide*, m. p. 173—174°, was obtained in poor yield.

(b) *From the methyl ester.* The procedure used for the *cis*-isomeride, but with heating for about 6 hours at 180—200°, gave a very dark product (0·7 g. from 1·4 g.), m. p. 166—167°, which after repeated crystallisation from methyl alcohol formed fine needles, m. p. 178·3—178·9° (Found : N, 6·1. $C_{15}H_{19}O_2N$ requires N, 6·0%).

trans-2-*Acetoxy*cyclo*hexane*-1-*carboxylic Acid.*—To 5 g. of acid, m. p. 111°, dissolved in 50 g. of pure pyridine, were added 15 g. of acetyl chloride, with stirring and efficient cooling. After 5 hours the mixture was treated, while cooling, with 30% sulphuric acid until acid to Congo-red, and extracted several times with ether. The ethereal extract was washed twice with cold water, dried, and distilled, first at atmospheric pressure and finally in a vacuum. The resulting oil crystallised on addition of a little ether and light petroleum, and when recrystallised from ether–light petroleum yielded prisms, m. p. 104·5—105·5° (corr.) (4·8 g.).

trans-2-*Acetoxy*cyclo*hexane*-1-*carboxy*-p-*toluidide.*—5 G. of the above acetyl derivative, dissolved in 30 ml. of benzene, were mixed with thionyl chloride, and the whole heated on a steam-bath for *ca.* 1 hour. The solvent and the thionyl chloride were removed by distillation, first at ordinary pressure and then in a vacuum. The residue was dissolved in ether (*ca.* 15 ml.), and *p*-toluidine (10 g.) in ether (*ca.* 50 ml.) was added with cooling. The mixture was set aside for a few hours, and the ethereal solution then treated with 10% hydrochloric acid and twice with water (if necessary, more ether was added, as the product is sparingly soluble in that solvent), decolorised with a little carbon black, filtered, and dried. The crystalline p-*toluidide* (*ca.* 4 g.) obtained on removal of the solvent was recrystallised several times from absolute methyl alcohol and then had m. p. 154·5—155·5° (corr.) (mixed m. p. with the *cis*-form, 124—145°) (Found : N, 5·3. $C_{15}H_{21}O_2N$ requires N, 5·1%).

The above compound (1·9 g.) was added to 5N-methanolic potassium hydroxide (50 ml.) and set aside overnight. The mixture was then diluted with the same volume of water, and the resulting precipitate filtered off, repeatedly washed with water, and recrystallised from absolute methyl alcohol. The product was shown by its m. p. and mixed m. p. to be *trans-cyclo*hexan-2-ol-1-carboxy-*p*-toluidide.

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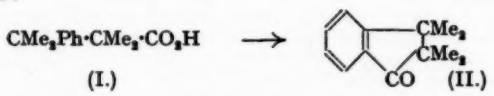
414. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part I. The Cyclisation of Tertiary Aromatic Acid Chlorides.*

By Eugene Rothstein and Rowland W. Saville.

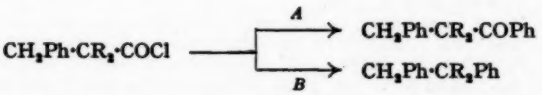
When tertiary acid halides are used in the Friedel–Crafts reaction, they afford, in general, hydrocarbons with the simultaneous liberation of carbon monoxide (Rothstein and Saboor, *J.*, 1943, 425). On the other hand, aryl-αα-dialkyl-propionic and -butyric acid derivatives yield the cyclic ketones normally expected. Experiments indicate that this is probably the result of the juxtaposition of the acyl group with a reactive point on the aromatic nucleus and not the influence of the phenyl group through the carbon chain. If the length of this chain is decreased, or if the nucleus is deactivated by the usual *meta*-directing groups, tertiary acid halides alkylate the aromatic compound, losing carbon monoxide, whilst primary acid derivatives are recovered unchanged. It is concluded that of the three possible reactions, *i.e.*, cyclisation, acylation, or alkylation, the preferred course for aryl tertiary acids is the first.

This group of papers embodies the results of a preliminary enquiry into the stability of the group CRR'R''·CO– and is based on the observation made by Rothstein and Saboor (*J.*, 1943, 425), that tertiary aliphatic acid derivatives eliminate carbon monoxide when mixed with aluminium chloride. That paper dealt more specifically with the acid anhydrides, but it was evident that the halides would, in general, behave in the same way and that with suitable changes the mechanisms there put forward would be equally applicable. It may be stated parenthetically that it is not intended necessarily to limit the investigations either to the Friedel–Crafts reaction or to acid chlorides; nevertheless as is elaborated more fully in Part V, the reaction whereby an acid chloride affords either a ketone or a hydrocarbon accompanied by the loss of carbon monoxide forms a convenient criterion for assessing the stability of the acyl group since it can be followed quantitatively as well as qualitatively. Before commencing a detailed study it became necessary to review the different aspects of the field owing to the great number of largely disconnected phenomena involved. One of them is the subject of this communication, whilst its complement is dealt with in Part II. Parts III and IV describe certain kinetic measurements. The correlation of these results with those of other investigators as well as some of the theoretical implications are deferred to Part V; for this reason any discussion in the first four papers is limited to the particular problem.

In their paper, Rothstein and Saboor had noted the inability of a *tertiary aliphatic* acid anhydride to yield a ketone with benzene; at that time no extension to the aromatic series had been made, though there was a reference to the cyclisation of β-phenyltetramethylpropionic acid (I) by sulphuric acid:



and in fact good yields of the corresponding hydrindones are obtained when the β-phenyl-αα-dialkylpropionyl chlorides are treated with aluminium chloride (Haller and Bauer, *Ann. Chim.*, 1921, [ix], **16**, 340) and similarly for the derivatives of γ-phenyl- and γ-naphthyl-αα-dialkylbutyric acids (Sen Gupta, *J. pr. Chem.*, 1938, **151**, 82; 1939, **152**, 9; *J. Indian Chem. Soc.*, 1934, **11**, 389). When benzene is substituted for ligroin as solvent, the experiments of Haller and Bauer have been repeated with substantially the same results; little carbon monoxide was liberated and products corresponding to neither of the reactions *A* nor *B* were isolated:



Hence it is to be inferred that the rate of cyclisation is very much greater than in either of these reactions. The experimental evidence of the present paper indicates that one of the principal factors leading to these "anomalous" results is the well-known ease with which five- and six-membered rings are formed, and perhaps the scarcely less important activation of the benzene ring by the aliphatic side-chain. If ring-formation is precluded by shortening the side-chain, then neither the cyclic nor the open-chain ketone is obtained. As a result aluminium

chloride reacts with a benzene solution of α-phenyl*iso*butyryl chloride to give a mixture of *iso*propylbenzene and 2 : 2-diphenylpropane :

$$CMe_2Ph\cdot COCl \longrightarrow \begin{cases} \longrightarrow CHMe_2Ph \\ \longrightarrow CMe_2Ph_2 \end{cases} + CO + Cl^{\ominus}$$

Similarly, αα-diphenylpropionyl chloride affords 1 : 1-diphenylethane and a hydrocarbon, m.p. 143°, isomeric with triphenylethane. The yields of carbon monoxide in the two experiments were 85% and 86%, respectively. Triphenylacetyl chloride furnished rather less carbon monoxide, the crystalline product yielding triphenylmethane when reduced.

The broad inference is clearly that the retention of the carbonyl group when cyclisation occurs is not due to the influence of the phenyl groups, since an increase in their number does not lead to the formation of a ketone. On the contrary, it is shown in Part V that they have an opposite effect. We also show later that the production of a ketone is not inevitable, even when carbon monoxide is not evolved. Furthermore, so far as cyclisation is concerned, activation of the ring is not a primary factor, otherwise the interaction of two or more molecules should have resulted in a ketone.

$$2CMe_2Ph\cdot COCl \longrightarrow CMe_2Ph\cdot CO\cdot C_6H_4\cdot CMe_2\cdot CO\cdot \ldots$$

To test the remaining possibility, namely that a phenyl group in a β- or a γ-position might stabilise the acyl group, p-*nitrophenylpivaloyl* and γ-2 : 4-*dinitrophenyl-αα-dimethylbutyryl chloride*, *p*-$NO_2\cdot C_6H_4\cdot CH_2\cdot CMe_2\cdot COCl$ and 2 : 4-$(NO_2)_2C_6H_3\cdot CH_2\cdot CH_2\cdot CMe_2\cdot COCl$, respectively, were prepared. It was considered that a nitro-group, whilst deactivating the nucleus, would at the same time favour the retention of the carbonyl group (although the $-I$ effect, relayed through the carbon chain, would be largely damped down). Hoyer (*J. pr. Chem.*, 1934, **139**, 94) succeeded in cyclising β-*o*-nitrophenylpropionyl chloride in carbon disulphide, but the *p*-nitro-derivative was recovered unchanged (Ingold and Piggott, *J.*, 1923, 1469). When we repeated their experiment in benzene solution, neither ω-*p*-nitrobenzylacetophenone nor 4-nitrodibenzyl resulted, and unlike the above authors we were unable to isolate any *p*-nitrophenylpropaldehyde. Repetition in carbon disulphide solution yielded a sulphur-containing substance, the melting point of which was considerably higher than that recorded by Ingold and Piggott for 6-nitro-1-indan-1-one prepared by a different method.

As expected, *p*-nitrophenylpivaloyl chloride eliminated carbon monoxide forming 2-*phenyl*-1-p-*nitrophenyl*isobutane

$$p\text{-}NO_2\cdot C_6H_4\cdot CH_2\cdot CMe_2\cdot COCl \longrightarrow p\text{-}NO_2\cdot C_6H_4\cdot CH_2\cdot CPhMe_2 + CO$$

and similarly, the dinitro-acid chloride afforded 2-*phenyl*-4-2′ : 4′-*dinitrophenyl*-2-*methylbutane* :

$$2 : 4\text{-}(NO_2)_2C_6H_3\cdot CH_2\cdot CH_2\cdot CMe_2\cdot COCl \longrightarrow 2 : 4\text{-}(NO_2)_2C_6H_3\cdot CH_2\cdot CH_2\cdot CPhMe_2 + CO$$

We therefore conclude that of the three possibilities, namely cyclisation, ketone formation, or decomposition, in the absence of any specific factor that may hinder one of them, the preferred course in the case of arylated *tertiary* acids is the first. The second occurs only in specially favourable conditions, and forms the subject of Part II of this series. It may be noticed that elimination of carbon monoxide is not always followed by combination with the aromatic component; the alkylated phenylacetic acid chlorides yield in addition a small proportion of the hydrocarbon which would result from the decarboxylation of the acid; however, as judged from the volume of carbon monoxide isolated, its presence should be attributed to a secondary reaction. The matter is discussed further in Part V.

Experimental.

Apparatus.—The Friedel–Crafts reactions described in this and the succeeding papers were carried out in a three-necked flask fitted with a mercury-sealed stirrer, a reflux condenser, and a ground-in dropping funnel, by means of which the acid halide could be run in. For experiments in which the solid catalyst was added to a solution of the acid derivative, the funnel was replaced by a ground joint connected to the neck of a distilling flask by means of wide-bore pressure tubing; this flask, through the side-arm of which dry nitrogen could be passed, contained the catalyst, and the latter could be added in small portions to the reaction mixture. A delivery tube from the top of the condenser led through a calcium chloride guard-tube to 1-l. measuring cylinders which were inverted over water. Before the start of the reaction, the whole apparatus was swept through with dry nitrogen, and again after its completion.

Determination of Carbon Monoxide.—The evolved gases were kept over water for 1 day, and a measured volume washed with, successively, water, concentrated potassium hydroxide solution, and bromine water. The residual gas was then shaken with a freshly prepared ammoniacal cuprous chloride solution contained in a Hempel pipette until no further contraction in volume took place. Lastly it was shaken

again with a fresh solution of the reagent to confirm the completeness of the absorption of the carbon monoxide.

Preparation of the Substituted Acetic Acids.

α-Phenylisobutyric Acid.—Benzyl cyanide was methylated by methyl iodide and freshly prepared sodamide obtained by dissolving sodium in liquid ammonia in the presence of hydrated ferric nitrate (Haller and Bauer, *Compt. rend.*, 1912, **155**, 1582; Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120), and the 2-phenyl-2-propyl cyanide so obtained was hydrolysed. Other methods for the preparation of this acid offered no advantage. Phenyldimethylcarbinol, for instance, could not be converted into the cyanide owing to elimination of hydrogen chloride from the intermediate chloride on distillation or when mixed with a metallic cyanide; in either case *iso*propenylbenzene, b.p. 60—61°/17 mm., was formed (Found: C, 91·3; H, 8·7. Calc. for C_9H_{10}: C, 91·5; H, 8·5%). On the other hand, a Friedel–Crafts condensation of ethyl α-bromo*iso*butyrate with benzene (Wallach, *Chem. Zentr.*, 1899, II, 1047) afforded not more than a 19% yield which was smaller when the ester was replaced by acid (Brander, *Rec. Trav. chim.*, 1918, **37**, 681).

1 : 1-*Diphenylpropionic Acid.*—2 : 2-Diphenylpropaldehyde, obtained by the rearrangement of 1 : 2-diphenylpropane-1 : 2-diol (Tiffineau and Dorlencourt, *Ann. Chim.*, 1909, [viii], **16**, 254) with 20% sulphuric acid (yield 54%), was oxidised by alkaline potassium permanganate (yield 53%). Warming an ethereal solution of the acid with thionyl chloride and a drop of pyridine gave a 72% yield of the acid chloride.

Triphenylacetic acid, obtained by passing carbon dioxide through ethereal triphenylmagnesium chloride (Gilman, *J. Amer. Chem. Soc.*, 1929, **51**, 1576, 3493; Rule and Bain, *J.*, 1930, 1901), was converted into the acid chloride with thionyl chloride (yield 82%).

β-Phenyl-αα-dialkylpropionic Acids.—The best methods for the preparation of these acids were those of Haller and Bauer (*loc. cit.*) and are outlined below. In order to confirm the location of the alkyl groups, however, other methods leading to unambiguous structures were initially employed.

(i) An ethereal solution of benzoyl chloride was condensed with the sodio-derivatives of the appropriate dialkylacetic esters prepared by the use of sodio-triphenylmethane (Hudson and Hauser, *J. Amer. Chem. Soc.*, 1941, **63**, 3156; *Org. Synth.*, Coll. Vol. 2, p. 269, note 2; p. 609, note 3), the yield of the benzoyl esters being 60%. The Clemmensen reduction in a hydrocarbon solvent (compare Martin, "Organic Reactions," Vol. 1, p. 155), followed by fractionation through an electrically heated, packed column, yielded the esters (50%) which were hydrolysed to the required acids by alcoholic potash.

(ii) A Reformatsky condensation of trioxymethylene with ethyl α-bromo*iso*butyrate was accomplished by a modification of the method of Blaise and Marcilly (*Bull. Soc. chim.*, 1904, [iii], **31**, 110). A three-necked flask fitted with a mercury-sealed stirrer and a condenser was connected to a flask containing the trioxymethylene. Dry benzene (120 g.), zinc turnings (35 g.), and the bromo-ester (40 g.) were placed in the main flask, and to them was added a mixture of the reactants in a test-tube, the reaction having been started by warming. The main bulk was now warmed gently and a further quantity of the ester (40 g.) added. The trioxymethylene (12 g.) contained in the external flask was vapourised, by heating the latter in an oil-bath, at such a rate as to maintain a moderate reaction. After the product had been boiled for 30 minutes and set aside overnight, it was mixed with a slight excess of dilute acid, and the benzene layer separated, washed with dilute ammonia to remove unchanged trioxymethylene, and dried (Na_2SO_4). The ethyl hydroxypivalate (yield 51%) was then hydrolysed and the acid mixed with six times its weight of hydrobromic acid, saturated at 0°. The liquid was warmed for 10 hours at 80° and a further 10 hours at 100° (McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 806; Kohn and Schmidt, *Monatsh.*, 1904, **25**, 1056). The bromo-acid (yield 59%) was re-esterified and condensed with benzene, using aluminium chloride. The maximum yield obtainable was, however, 12%.

(iii) The steps in Haller and Bauer's synthesis consist of the alkylation of indan-1-one by the appropriate alkyl halide in conjunction with sodamide, the latter reagent also being used for breaking the ring and yielding the phenyldialkylpropionamide; finally the acid is prepared by the action of nitrous acid. Use of freshly prepared solutions of sodamide in liquid ammonia instead of the usual suspension of the powdered reagent for both the alkylations and for ring-fission resulted in greatly improved yields. The phenylpivalic acid was obtained in this way in 83% yield from the amide, and crystallised in white needles, m. p. 57° (Found: C, 74·1; H, 7·9. Calc. for $C_{11}H_{14}O_2$: C, 74·1; H, 7·8%). It was identical (m. p. and mixed m. p.) with the specimens prepared by the first two methods. Very much the same yields were isolated of the diethyl homologue.

β-p-Nitrophenylpivalic Acid.—The direct interaction of *p*-nitrobenzyl chloride with the Grignard compound of ethyl α-bromo*iso*butyrate failed and consequently this acid was prepared by the nitration of phenylpivalic acid. The acid (1 g.) was heated on the steam-bath with concentrated nitric acid (1 c.c.) for 3 hours and then mixed with ice. The yellow solid was crystallised twice from ethyl acetate, whence it separated in pale lemon-coloured plates, m. p. 134° (Found: C, 58·7; H, 5·8; N, 5·6. $C_{11}H_{13}O_4N$ requires C, 59·1; H, 5·8; N, 6·2%). This *β-p-nitrophenylpivalic acid* is identical with that obtained by Haller and Bauer as a by-product in the decomposition of phenylpivalamide to the acid, but these workers failed to orient their product. The above structure follows from the formation of *p*-nitrobenzoic acid on oxidation.

γ-2 : 4-Dinitrophenyl-αα-dimethylbutyric Acid.—β-Benzoyl-αα-dimethylpropionic acid (4 g.) was reduced with zinc amalgam (20 g.), water (12 c.c.), concentrated hydrochloric acid (30 c.c.), and toluene (15 c.c.) (yield 74%). The product was heated with three times its weight of concentrated nitric acid on the steam-bath for 2½ hours, and the *γ-2 : 4-dinitrophenyl-αα-dimethylbutyric acid* precipitated with ice–water; this acid separated from ethyl acetate–ligroin in prisms, m. p. 111° (Found: C, 51·2; H, 4·9; N, 9·3. $C_{12}H_{14}O_6N_2$ requires C, 51·1; H, 4·9; N, 9·8%). 2 : 4-Dinitrobenzoic acid was obtained on oxidation.

γ-4-Methoxy-3-diphenylylbutyric Acid.—4-Aminodiphenyl was diazotised (Schlenk, *Annalen*, 1909, **368**, 303; Kaiser, *ibid.*, 1890, **257**, 101), and the mixture was boiled to yield the phenol (76%). Methylation with alkali and methyl sulphate yielded 4-methoxydiphenyl from which *γ*-keto-*β*-4-methoxy-3-

diphenylylbutyric acid was obtained by treatment with succinic anhydride and aluminium chloride (Fieser and Bradsher, *J. Amer. Chem. Soc.*, 1936, **58**, 1738). The methyl ester was then reduced by the ordinary Clemmensen method. The acid chloride did not react with aluminium chloride and benzene.

β-Mesitoylpivalic Acid.—Aluminium chloride (24 g., 2·1 mols.) was added in small portions to a stirred mixture of *as*-dimethylsuccinic anhydride (10 g.) and mesitylene (39 g.) at 0°. The mixture was heated very gradually until the temperature reached 80—100° and maintained there for 1 hour. A white solid (crude yield, 21 g.) was isolated from the resulting dark red complex. *β-Mesitoylpivalic acid* separated from ligroin in small white crystals, m. p. 105—106° (yield, 70%) (Found: C, 72·3; H, 7·9. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·0%). It was not possible to reduce the acid.

Reactions of Acid Chlorides.

Cyclisation of Phenylpivaloyl and 3-Benzylpentane-3-carboxyl Chloride.—By use of benzene and 2 molecules of aluminium chloride, 66% and 73% yields, respectively, of the corresponding 2 : 2-dialkylindan-1-ones were obtained (Haller and Bauer employed 1·1—1·2 mols. of the catalyst, ligroin being the solvent; the yield in each case was 80%). The yields of carbon monoxide were 2·5% and 3·5% for the two reactions.

Reaction of p-*Nitrophenylpivaloyl Chloride with Benzene.*—*p*-Nitrophenylpivalic acid (10 g.) was converted into the acid chloride by purified thionyl chloride (9 g.). Excess of the reagent was removed by heating the mixture to 100° in a vacuum, and then thiophen-free benzene (80 c.c.) was added, followed by resublimed aluminium chloride (15 g.) in small portions. The liquid was then boiled under reflux for 3 hours. Carbon monoxide (347 c.c., 44·5%) was evolved. The liquid product containing much tarry material was identified as 2-*phenyl*-1-p-*nitrophenylisobutane* since nitration with a mixture of fuming nitric acid and concentrated sulphuric acid gave the 2 : 2′ : 4 : 4′-*tetranitro*-compound which crystallised from ethyl acetate in pale yellow plates, m. p. 250—251° (Found: C, 48·9; H, 3·6; N, 13·7. $C_{16}H_{14}O_8N_4$ requires C, 49·2; H, 3·6; N, 14·2%). Oxidation afforded 2 : 4-dinitrobenzoic acid. Moreover, 1 : 2-diphenyl*iso*butane, synthesised from *iso*butene dibromide, benzene, and aluminium chloride (Bodreaux, *Compt. rend.*, 1901, **132**, 1335), was nitrated to the identical tetranitro-compound.

Reaction of γ-2 : 4-Dinitrophenyl-αα-dimethylbutyryl Chloride with Benzene.—The acid chloride, prepared from the acid (8·4 g.) with thionyl chloride, was dissolved in benzene (80 c.c.), and aluminium chloride (2·5 mols.) added. The resulting 2-*phenyl*-4-2′ : 4′-*dinitrophenyl*-2-*methylbutane* separated from ethyl acetate in pale yellow prisms, m. p. 135° (Found: C, 65·0; H, 5·8; N, 9·3. $C_{17}H_{18}O_4N_2$ requires C, 64·9; H, 5·6; N, 8·9%). The yield of carbon monoxide was 51·5%.

Attempted Cyclisation of 2-p-*Nitrophenylpropionyl Chloride.*—The acid chloride (from 5 g. of acid) was boiled for 1 hour with benzene (60 c.c.) and aluminium chloride (1·2 mols.). About 81% of the original acid was recovered unchanged. The carbon monoxide eliminated corresponded to 2·5% of that theoretically possible. Repetition in carbon disulphide solution afforded a substance containing sulphur as well as nitrogen, and separating from absolute alcohol in white leaflets, m. p. 128—129° (Found: C, 59·5, 59·6; H, 4·2, 4·0; N, 4·9; S, 12·2%). Repeated recrystallisation failed to remove the sulphur.

Condensation of α-Phenylisobutyryl Chloride with Benzene.—A suspension of aluminium chloride (13·5 g., 1·5 mols.) in benzene (120 c.c.) was stirred at room temperature during the gradual addition of the acid chloride (12·3 g.) in the same solvent. Immediate evolution of gas took place, and stirring was continued for a further 2 hours. The following products of the reaction were identified. (i) *iso*Propylbenzene, b. p. 60—65°/20 mm. (yield, 1·2 g., 15%) (Found: C, 90·0; H, 9·9. Calc. for C_9H_{12}: C, 90·0; H, 10·0%), identified by comparison (m. p. and mixed m. p.) of its trinitro-derivative with that of cumene. (ii) 2 : 2-Diphenylpropane, b.p. 180—185°/12 mm. (yield, 6 g., 45%), not obtained pure (Found: C, 89·3; H, 7·9. Calc. for $C_{15}H_{16}$: C, 91·8; H, 8·2%); the *dinitro*-derivative, recrystallised from ethyl acetate and ligroin, had m. p. 133—134° (Found: C, 62·7; H, 5·1; N, 9·5. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9; N, 9·8%). (iii) A small quantity of unidentified residue, b. p. above 200° (decomp.)/0·1 mm. No trace of α-phenyl*iso*butyrophenone could be detected. The yield of carbon monoxide was nearly 85%.

Condensation of αα-Diphenylpropionyl Chloride with Benzene.—The reaction carried out in the same way as the previous experiment, with aluminium chloride (7 g., 1·8 mols.), benzene (100 c.c.), and αα-diphenylpropionyl chloride (7 g.), furnished an orange-red complex, carbon monoxide being rapidly liberated. The following products were isolated. (i) αα-Diphenylethane, b. p. 97—98°/0·2 mm. (yield, 1·7 g., 32·6% theory) (Found: C, 92·8; H, 7·3. Calc. for $C_{14}H_{14}$: C, 92·3; H, 7·7%). Nitric acid in acetic acid solution afforded the dinitro-derivative, m. p. 148° (Anschütz and Romig, *Ber.*, 1883, **18**, 664, 935; *Annalen*, 1886, **233**, 340), whilst oxidation by chromic acid gave benzophenone. (ii) A *hydrocarbon*, b. p. 180—220°/0·6 mm., separating from ethyl alcohol in small crystals, m. p. 143—144° (yield, 2·5 g.). The empirical formula, $C_{10}H_9$, is the same as that for triphenylethane, but the m. p. is very much greater than that of either of the isomers [Found: C, 93·0; H, 7·0. $(C_{10}H_9)_x$ requires C, 93·0; H, 7·0%]. The yield of carbon monoxide was 86%.

Condensation of Triphenylacetyl Chloride with Benzene.—Aluminium chloride (5·1 g., 2 mols.) was added in small portions to a stirred solution of triphenylacetyl chloride (5·9 g.) in benzene (80 c.c.), the mixture being cooled in ice. The yield of carbon monoxide was 59%. The substance isolated crystallised from alcohol as a white solid, m. p. 80°. This could correspond to the labile form of triphenylmethane, m. p. 81°, and oxidation with nitric acid (Schwartz, *Amer. Chem. J.*, 1904, **31**, 848) yielded pure triphenylcarbinol. Analysis of the compound, m. p. 80°, indicated that it could possibly be a mixture of the hydrocarbon and the carbinol (Found: C, 87·1; H, 6·6. Calc. for $C_{19}H_{16}$: C, 93·4; H, 6·6%) and in fact reduction of an alcoholic solution with tin and hydrochloric acid furnished pure triphenylmethane, m. p. 92—93°.

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415. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part II. The Acylation of Benzene Derivatives by Tertiary Acid Chlorides.*

By Eugene Rothstein and Rowland W. Saville.

Derivatives of aliphatic tertiary acids usually alkylate benzene in the presence of aluminium chloride, but by the choice of a suitable aromatic compound it is possible to synthesise the ketone. p-*Methoxyphenyl* tert.-*butyl ketone* is obtained, for example, when pivaloyl chloride is condensed with anisole, and analogous products result from other tertiary acid halides and anhydrides. When the alkylbenzenes are used, mixtures of ketone and hydrocarbon are formed, the ratio of the two depending partly on the proportion of catalyst present and partly on the nature of the alkyl groups. The yield of ketone is greatest with toluene and ethylbenzene, and least with *tert.*-butylbenzene. It is believed that hyperconjugation involving the methyl and ethyl groups provides a reasonable explanation of these last results (Part V).

The cyclisation, to cyclic ketones, of certain aryl-substituted tertiary acid chlorides shows that in favourable conditions the preferential reaction for this class of acid derivatives is acylation rather than alkylation. The main factor facilitating the first of these reactions is the contiguity of the end of the chain to the aromatic nucleus, one of minor importance being its activation (Part I, preceding paper). It is evident that the former condition is not available for straight-chain acylation, but by the employment of a suitably substituted aromatic compound it should be possible to overcome the difficulty. This has been realised, and experiments are now described leading to the successful preparation of ketones where in normal circumstances alkylation would be the expected result.

Pivaloyl chloride which has been used for the greater part of the work reacts similarly to the anhydride. There is, however, the difference, that whereas the latter requires the presence of more than one molecule of the catalyst, in the case of the acid halides only " catalytic " quantities are necessary. Neither derivative reacts in the absence of a catalyst; and the anhydride is unchanged when only 0·1 mol. aluminium chloride is used. Pivaloyl chloride on the contrary condenses with benzene in the presence of this molecular proportion of catalyst, and at least 66% of *tert.*-butylbenzene is formed though the speed of the reaction is noticeably less. This aspect is the main topic of Part III, but it should be remarked that in the case of ketone formation, as is generally known, the extent is dependent on the proportion of aluminium chloride initially used, quite irrespective of whether or not simultaneous alkylation takes place.

There are a few examples known where the type of product formed in a Friedel–Crafts reaction differs with the nature of the aromatic component, but the generality of, and the reason for, this phenomenon do not appear to have been recognised. It is not, in this paper, proposed to discuss the matter in detail, but it is appropriate to outline the relevant reactions of oxalyl chloride because of their importance to the present problem. A carbon disulphide solution of oxalyl chloride and benzene affords benzophenone when aluminium chloride is added. On the other hand, the addition of the halide to a cooled mixture of the other components yields benzoyl chloride and very little benzophenone (Staudinger, *Ber.*, 1908, **41**, 3558). By the use of anisole (*idem, ibid.*, 1912, **45**, 1594) and other phenolic ethers (Mitter and Mukherjee, *J. Indian Chem. Soc.*, 1939, **16**, 393; Staudinger, Schlenker, and Goldstein, *Helv. Chim. Acta*, 1921, **4**, 334) the substituted benzils are obtained. These authors do not mention the evolution of carbon monoxide in the course of their reactions, though Staudinger in his first paper did notice that a solution of oxalyl chloride in carbon disulphide eliminates the gas when treated with aluminium chloride. No mechanism was suggested beyond citing the decomposition of the acid chloride by water which he considered took place with the intermediate formation of oxalic anhydride:

$$ClCO{-}COCl \longrightarrow ClCO{-}CO{\cdot}OH \longrightarrow CO\overset{O}{\frown}CO \longrightarrow CO + CO_2$$

This does not appear to be a very satisfactory formulation and for reasons given in Part V it is suggested that the mechanism for the production of the acid chloride and ketone, and the benzil, respectively, involves two different routes:

$$(COCl)_2 \xrightarrow{C_6H_6} CO + HCl + Ph{\cdot}COCl \xrightarrow{C_6H_6} COPh_2 + 2HCl$$
$$(COCl)_2 \xrightarrow{PhOR} (RO{\cdot}C_6H_4{\cdot}CO)_2 + 2HCl$$

It is now found that all the *tertiary* acid chlorides so far examined yield the corresponding ketone when condensed with anisole; it is necessary in these cases to use more than one molecule of aluminium chloride:

$$CR_3{\cdot}COCl + PhOMe \longrightarrow CR_3{\cdot}CO{\cdot}C_6H_4{\cdot}OMe + HCl$$

Table I summarizes the results of the reactions of anisole with various acid halides. In each case the ketone was the only product.

TABLE I.

Condensation of Acid Halides with Anisole.

Acid.	Solvent.	Product.	Yield, %.
Pivalic	Ligroin	p-*Methoxyphenyl* tert.-*butyl ketone*	79·6
Pivalic	CS_2	,, ,, ,,	45
Tetramethylsuccinic (anhydride)	CS_2	β-p-*Anisoyl*-αα*β-trimethylbutyric acid*	54
α-Phenyl*iso*butyric	Ligroin	*p*-Methoxyphenyl 2-phenyl-2-propyl ketone	71
αα-Diphenylpropionic	CS_2	p-*Methoxyphenyl* 1 : 1-*diphenylethyl ketone*	64
1-Methyl*cyclo*pentanecarboxylic (IV)	Ligroin	p-*Methoxyphenyl* 1-*methyl*cyclo*pentyl ketone* (VI)	60·5

It may be remembered that α-phenyl*iso*butyryl and αα-diphenylpropionyl chloride yield hydrocarbons with benzene (Part I), whilst tetramethylsuccinic anhydride affords β-phenyl-αα*β*-trimethylbutyric acid (Rothstein and Saboor, *J.*, 1943, 425).

We have re-examined the reactions of *cyclo*pentane derivatives because Saboor (*J.*, 1945, 922) claimed to have isolated both methyl 1-phenyl*cyclo*pentylacetate (II) (yield, 95%) and methyl 1-benzoyl*cyclo*pentylacetate (III) (yield not stated) from the acid chloride of methyl 1-carboxy*cyclo*pentylacetate (I):

$$\underset{\text{(I.)}}{ClOC{\cdot}C(<C_4H_8){\cdot}CH_2{\cdot}CO_2Me} \longrightarrow \underset{\text{(II.)}}{Ph{\cdot}C(<C_4H_8){\cdot}CH_2{\cdot}CO_2Me} + \underset{\text{(III.)}}{Ph{\cdot}CO{\cdot}C(<C_4H_8){\cdot}CH_2{\cdot}CO_2Me}$$

The formation of the benzoyl compound (III) is unusual when a *tertiary* acid halide reacts with benzene. The only instances which have been encountered by the present authors are the formation of trichloroacetophenone from trichloroacetyl chloride, and the small quantity of benzil reported to be isolated when oxalyl bromide is treated in benzene with aluminium bromide (Staudinger, *Ber.*, 1912, **45**, 1599). Repeating Saboor's condensation we have been unable to detect any ketone, though the yield of hydrocarbon was rather less than his (79%). On the other hand, the very high yield of carbon monoxide (89%) did not indicate appreciable ketone formation. It is possible that Saboor's ester contained a small quantity of the isomeric 1-carbomethoxy*cyclo*pentylacetyl chloride, $MeO_2C{\cdot}C(<C_4H_8){\cdot}CH_2{\cdot}COCl$. Nevertheless, envisaging the possibility that the *cyclo*pentyl group might facilitate ketone formation, 1-methyl-*cyclo*pentane-1-carboxyl chloride (IV) was condensed with benzene; here again no ketone was formed, the only product being 1-*phenyl*-1-*methyl*cyclo*pentane* (V):

$$\text{(IV.)}\quad (C_4H_8>)CMe{\cdot}COCl \xrightarrow[PhOMe]{C_6H_6} \begin{cases} (C_4H_8>)CPhMe & \text{(V.)} \\ (C_4H_8>)CMe{\cdot}CO{\cdot}C_6H_4{\cdot}OMe & \text{(VI.)} \end{cases}$$

With anisole the expected ketone (VI) was produced.

Since in the cyclisations mentioned in Part I, the activating groups is the side-chain itself, the next consideration was the possibility that the homologues of benzene might be sufficiently reactive for ketone formation to occur. It had previously been found (Rothstein and Saboor, *J.*, 1943, 425) that tetramethylsuccinic anhydride affords β-*p*-tolyl-αα*β*-trimethylbutyric acid and no ketone. In the present work we describe the first examples where appreciable quantities of both ketone and hydrocarbon have been produced simultaneously: pivaloyl chloride is converted into a mixture of approximately equal parts of *p-tert.*-butyltoluene and of p-*tolyl* tert.-*butyl ketone*, together with a small quantity of impure material which appeared to be mainly the *ortho*-isomeride. Ethylbenzene and *tert.*-butylbenzene behaved similarly, but neither acetanilide nor diphenyl gave rise to ketonic products though the electromeric effect of the former is similar to that of anisole. The *tert.*-butyldiphenyl obtained from diphenyl was presumably the *para*-isomeride, but we were unable to isolate a crystalline substance, m. p. 53°, which Grosse, Mavity, and Ipatieff prepared in 5% yield from *p*-bromo-*tert.*-butylbenzene and phenyl-lithium (*J. Org. Chem.*, 1939, **3**, 448).

Table II and III show the proportions of ketone and hydrocarbon obtained with excess of hydrocarbon (or anisole) or of carbon disulphide, respectively, as solvent. In every case more than one molecule of aluminium chloride was used. When less than one molecule of the catalyst

TABLE II.

Condensations of Pivaloyl Chloride with Various Aromatic Derivatives in Excess.

Hydrocarbon.	Yield of products, %.	Proportion isolated of ketone, %.	Proportion isolated of hydrocarbon, %.	Yield of CO, %.
Benzene	67	0	100	87
Toluene	87 *	58·6	41·4	53
Ethylbenzene	78·5	62·9	37·1	50
tert.-Butylbenzene	—	26·3 †	—	65
Anisole	79·6	100	0	7

* Inclusive of 17% of *o*-tolyl *tert.*-butyl ketone.
† Percentage yield. The proportion of ketone could not be calculated (see Experimental section).

TABLE III.

Condensations of Pivaloyl Chloride with Various Hydrocarbons and Anisole in Carbon Disulphide.

Aromatic derivative.	Yield of products, %.	Proportion isolated of: ketones, %.	Proportion isolated of: hydrocarbon, %.	Yield of CO, %.
Ethylbenzene	66	42·4	57·6	68
tert.-Butylbenzene	71	0	100	75
Anisole	45	100	0	0

was used, the proportion of the ketone formed was considerably less; thus toluene afforded only 6·8% ketone when 0·1 mol. of catalyst was present.

In view of the liberation of carbon monoxide which occurs when pivalic acid or its chloride is heated with sulphuric acid at 135° (Bistrzycki, *Ber.*, 1907, **40**, 4370) or 100°, respectively (Boeseken, *Rec. Trav. chim.*, 1910, **29**, 85), a sulphuric-acid-catalysed reaction between pivalic acid and benzene was attempted. The greater part of the acid was recovered unchanged; the only other product was a very small quantity of an acid, m. p. 145°, which could not be identified. Campaigne and Suter (*J. Amer. Chem. Soc.*, 1946, **68**, 880) similarly found that in toluene the only reaction was sulphonation of the solvent.

EXPERIMENTAL.

Condensations of Pivalic Acid Derivatives.—(a) *With benzene.* (i) A stirred mixture of pivalic acid (20 g.), 75% sulphuric acid (30 c.c.), and benzene (31 g., 2 mols.) was boiled for 40 minutes. The yield of carbon monoxide was 41·5 c.c. (N.T.P.), corresponding to 0·95% of the acid used. About 93% of the acid was recovered, though it had the odour of *iso*butene polymers. After removal of the benzene, the original reaction mixture gradually deposited a colourless acid (0·4 g.), m. p. 145° (after crystallisation from benzene) (Found: C, 47·9; H, 7·9%; *M*, 396).

(ii) A stirred suspension of aluminium chloride (11·6 g., 1 mol.) in benzene (60 c.c.) was cooled in an ice-bath, and a solution of pivaloyl chloride (10 g.) in benzene added. The yield of carbon monoxide (1697 c.c.) was 86·9%. The main product, *tert.*-butylbenzene (67·2%), b. p. 63°/10 mm., was identified by conversion into the 2 : 4-dinitro-derivative (mixed m. p.) (Malherbe, *Ber.*, 1919, **52**, 321). 0·5 G. of a hydrocarbon, b. p. 105—110°/10 mm., possibly impure tri-*tert.*-butylbenzene was also isolated (Found: C, 87·2; H, 11·1. Calc. for $C_{18}H_{30}$: C, 87·8; H, 12·2%).

(iii) By use of 0·1 mol. of aluminium chloride, 66% of *tert.*-butylbenzene was obtained; the reaction was noticeably slower.

(iv) A mixture of pivalic anhydride (12 g.), benzene (50 c.c.), and aluminium chloride (0·86 g., 0·1 mol.) was warmed at 40° for 30 minutes. Approx. 31 c.c. of carbon monoxide were collected (5% yield); the product was a mixture of the anhydride and the acid, but no *tert.*-butylbenzene.

(b) *With toluene.* (i) The reaction was carried out at 0°, with pivaloyl chloride (7 g.), aluminium chloride (11·5 g., 1·5 mols.), and toluene (60 c.c.). It was completed over a period of 75 minutes, about half this time at room temperature. The yield of carbon monoxide was 53% (689 c.c. at N.T.P.). The liquid products were *p-tert.*-butyltoluene, b. p. 83°/15 mm. (3·1 g., 36%), identified by its dinitro-derivative, m. p. 96° (Auwers, *Ber.*, 1916, **49**, 2403), *p-tolyl* tert.-*butyl ketone*, a colourless liquid with a faint almond odour, b. p. 125°/17 mm. (3·0 g., 34·5%) (Found: C, 81·7; H, 9·1. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%) [the *semicarbazone*, prepared by heating the ketone (0·2 g.) for 10 minutes in a concentrated aqueous-alcoholic solution of semicarbazide hydrochloride (0·2 g.) and crystalline sodium acetate (0·3 g.), separated from alcohol in prisms, m. p. 185—186° (Found: C, 66·6; H, 7·8; N, 17·8. $C_{13}H_{19}ON_3$ requires C, 66·9; H, 8·1; N, 18·0%)], and *o-tolyl* tert.-*butyl ketone*, a colourless viscous liquid, b. p. 145—150°/14 mm. (17%) (Found: C, 82·7; H, 9·5. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%), from which no ketonic derivative could be obtained, whilst the analytical results indicated the presence of a small quantity of impurity.

(ii) The acid chloride (12·2 g.) was slowly added to the stirred mixture of the catalyst aluminium

chloride (1·35 g., 0·1 mol.) and toluene (70 c.c.) at room temperature. After 2 hours, the reaction was completed by boiling the liquid for the same period of time. The products were *p-tert.*-butyltoluene (9·8 g., 65%), *p*-tolyl *tert.*-butyl ketone (0·6 g., 3·4%), and *o*-tolyl *tert.*-butyl ketone (0·2 g., 1·2%) (the quantity was too small for effective purification (Found : C, 81·9; H, 9·8. Calc. for $C_{12}H_{16}O$: C, 81·8; H, 9·1%). The total quantity of the mixed ketones before fractionation was 1·2 g.

(c) *With* tert.-*butylbenzene.* The yield of hydrocarbon is uncertain particularly when excess of *tert.*-butylbenzene is used because reaction of the catalyst with the former may lead to the formation of *p*-di-*tert.*-butylbenzene and benzene. For this reason, the proportion of non-ketonic substances is of little significance. (i) Pivaloyl chloride (8·8 g.), *tert.*-butylbenzene (50 c.c.), and aluminium chloride (12·3 g.) were stirred for 1 hour at room temperature. The yield of carbon monoxide was 1073 c.c. (65%). Together with unchanged *tert.*-butylbenzene and di-*tert.*-butylbenzene, there was obtained p-tert.-*butylphenyl* tert.-*butyl ketone*, a colourless liquid, b. p. 100—102°/1·2 mm. (26·3%) (Found : C, 82·7; H, 10·2. $C_{15}H_{22}O$ requires C, 82·6; H, 10·1%).

(ii) In carbon disulphide solution. This experiment was carried out in the same way as the first with pivaloyl chloride (7·7 g.), alumium chloride (13 g., 1·5 mols.), *tert.*-butylbenzene (12·3 g., 1·1 mols.), and carbon disulphide (80 c.c.). Carbon monoxide in 75% yield, *tert.*-butyl- and di-*tert.*-butyl-benzene were formed. The latter hydrocarbon was identified by its m. p. (76°) and by conversion into the dinitro-derivative (plates m. p. 190°, from alcohol) with fuming nitric acid at room temperature.

(d) *With ethylbenzene.* (i) By use of pivaloyl chloride (9·2 g.), ethylbenzene (12·2 g., 1·5 mols.), aluminium chloride (15·3 g., 1·5 mols.), and carbon disulphide (100 c.c.), 1157 c.c. of carbon monoxide (68%), *p*-ethyl-*tert.*-butylbenzene, b. p. 102—105°/17 mm. (4·7 g., 38%) (Found : C, 88·7; H, 11·0. Calc. for $C_{12}H_{18}$: C, 88·9; H, 11·1%), and p-*ethylphenyl* tert.-*butyl ketone*, b. p. 85°/0·2 mm. (4·1 g., 28%) (Found : C, 82·5; H, 9·5. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%), were obtained. Both benzene derivatives furnished terephthalic acid when oxidised by chromic acid (cf. *Org. Synth.*, 1946, **26**, 95).

(ii) Slow addition of pivaloyl chloride (6 g.) to a suspension of aluminium chloride (10 g.) in ethylbenzene (60 c.c.) afforded carbon monoxide (616 c.c., 50%), *p*-ethyl-*tert.*-butylbenzene (2·6 g., 32%), and the above ketone (46·5%).

(e) *With anisole.* (i) The acid chloride (11·2 g.) in dry light petroleum (b. p. 60—80°; 20 c.c.) was added slowly to a stirred mixture of the catalyst (18·6 g., 1·5 mols.), anisole (20 g., 2 mols.), and light petroleum (100 c.c.) cooled in an ice-bath. After a further 45 minutes, the mixture was very gently warmed (to minimise the danger of any cleavage of the ether), and the resulting pink complex decomposed by acid. No more than 35 c.c. of carbon monoxide were collected (6·7%), and the p-*methoxyphenyl* tert.-*butyl ketone*, b. p. 138—140°/8 mm., was obtained in 79·6% yield (14·2 g.) (Found : C, 74·7; H, 8·2. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). The *semicarbazone* crystallised from absolute alcohol in plates, m. p. 150—151° (Found : C, 62·5; H, 7·5; N, 16·8. $C_{13}H_{19}O_2N_3$ requires C, 62·6; H, 7·6; N, 16·9%).

(ii) Condensation in carbon disulphide gave rather smaller yields (45%) of the ketone which in this case was coloured pink in spite of repeated distillations. Anisole, however, is known to yield products such as *p*-dithiocarbomethoxyphenol with carbon disulphide when aluminium chloride is present (Jorg, *Ber.*, 1927, **60**, 1466). This substance was not actually isolated, though traces of a liquid, b. p. 110—120°/15 mm., were present (Found : C, 66·1; H, 7·1%).

(f) *With acetanilide.* Aluminium chloride (12·3 g., 1·5 mols.) was added in small portions over a period of 30 minutes to a vigorously stirred mixture of pivaloyl chloride (7·4 g.), acetanilide (8·3 g.), and chloroform (60 c.c.) cooled in ice. The liquid was then boiled under reflux for 30 minutes. The carbon monoxide content of the liberated gases was 1397 c.c. (75·2%), whilst decomposition of the complex gave a liquid which solidified to a mixture of unchanged acetanilide and *p-tert.*-butylacetanilide. The latter being only sparingly soluble in boiling water was separated and crystallised from aqueous alcohol in shining white plates, m. p. 171—172° (55%) (Found : C, 75·7; H, 8·9; N, 6·9. Calc. for $C_{12}H_{17}ON$: C, 75·4; H, 8·9; N, 7·3%). No ketonic product could be detected.

(g) *With diphenyl.* The reaction was accomplished in carbon disulphide solution using 1·1 mols. of the catalyst. There was the usual immediate evolution of carbon monoxide, and a 62% yield of 4-*tert.*-butyldiphenyl, b. p. 110—115°/0·2 mm., which was separated from traces of unchanged diphenyl by fractional distillation, was obtained (Found : C, 90·9; H, 8·7. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%). Owing possibly to traces of isomerides it could not be induced to crystallise.

Condensations of cyclo*Pentane Derivatives.*—*The acid chloride* (I) *of methyl* 1-*carboxy*cyclo*pentyl-acetate.* The acid chloride (10 g.), prepared essentially by the method of Vogel (*J.*, 1928, 2010), was added to aluminium chloride (14 g., 2·1 mols.) and benzene (100 c.c.), the temperature being maintained below 10°. The products were carbon monoxide (89·2%) and methyl 1-phenyl*cyclo*pentylacetate (II), b. p. 118—120°/9 mm. (78·9%) (Found : C, 76·9; H, 8·5. Calc. for $C_{14}H_{18}O_2$: C, 77·4; H, 8·3%). No ketonic fraction, b. p. 190°/11 mm. (Saboor, *loc. cit.*), was present. There was a trace of residual oil, b. p. > 230°/0·2 mm., which was not examined.

1-*Methyl*cyclo*pentane*-1-*carboxyl chloride* (IV). 1-Methyl*cyclo*pentane-1-carboxylic acid (Meerwein, *Annalen*, 1914, **405**, 171; 1918, **417**, 263) was converted into the acid chloride by keeping it overnight with thionyl chloride (1·5 mols.), warming it for 15 minutes, and then distilling it. B. p. 61°/15 mm. Yield, 85%. The substitution of thionyl chloride for the phosphorus trichloride used by previous workers affords a much purer specimen of the acid chloride.

(i) The condensation was carried out at room temperature with the acid chloride (6 g.), aluminium chloride (8·1 g.), and benzene (50 c.c.). Carbon monoxide (322 c.c., 70·3%) and 1-*phenyl*-1-*methyl*cyclo*pentane* (V), b. p. 97°/10 mm. (67·4%) (Found : C, 89·9; H, 9·8. $C_{12}H_{16}$ requires C, 90·0; H, 10·0%), were the products.

(ii) Slow addition of the acid chloride (2·7 g.) in ligroin (10 c.c.) to a stirred mixture of anisole (6 g.), aluminium chloride (3 g., 1·2 mols.), and ligroin (50 c.c.) furnished 1-*methyl*cyclo*pentyl methoxyphenyl ketone* (VI), a thick colourless liquid, b. p. 145—150°/0·3 mm. (60·5%) (no ketonic derivative could be prepared) (Found : C, 77·2; H, 8·1. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·2%).

Other Condensations with Anisole.—(i) *Tetramethylsuccinic anhydride.* Anisole (7 g. 2 mols.) was added to a carbon disulphide solution of aluminium chloride (8·8 g., 2·1 mols.) and tetramethylsuccinic

anhydride (5 g.) at 0°, the temperature being raised gradually to the b. p. After 30 minutes the complex was decomposed in the usual manner affording *β-anisoyl-αα-trimethylbutyric acid* which crystallised from ethyl alcohol in plates, m. p. 185° (54%) (Found: C, 67·9; H, 7·5. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%). The *methyl* ester, prepared from the silver salt was an unusually sweet-smelling liquid, b. p. 135—140°/0·6 mm.; it solidified in a freezing mixture to a milky-white solid, m. p. 26°, which resisted all attempts at recrystallisation (Found: C, 68·6; H, 7·9. $C_{16}H_{22}O_4$ requires C, 69·0; H, 7·9%). β-Methoxyphenyl-ααβ-trimethylbutyric acid was not detected and the quantity of carbon monoxide eliminated was negligibly small. Tetramethylsuccinic anhydride was recovered unchanged from a similar condensation where the anisole was replaced by *tert.*-butylbenzene, but some di-*p*-*tert.*-butylbenzene was formed.

(ii) *α-Phenylisobutyryl chloride.* A ligroin solution of this chloride (4 g.) was allowed to react with aluminium chloride (4 g.), anisole (3·6 g.), and ligroin (60 c.c.). The product was *p*-methoxyphenyl 2-phenyl-2-propyl ketone, which crystallised from light petroleum (b. p. 60—80°) in small crystals, m. p. 99° (71%) (Found: C, 80·4; H, 7·0. Calc. for $C_{17}H_{18}O_2$: C, 80·3; H, 7·1%). The melting point, and those of the oxime (m. p. 194°) and the semicarbazone (m. p. 210°), agree with those obtained by Bruzau (*Compt. rend.*, 1932, **194**, 1662; *Ann. Chim.*, 1934, [ii], **1**, 257) who synthesised the ketone from *p*-methoxyphenylmagnesium bromide and α-phenylisobutyramide.

(iii) *αα-Diphenylpropionyl chloride.* The reagents used were the acid chloride (7 g.), aluminium chloride (7 g., 2 mols.), and anisole (6·2 g., 2 mols.) in carbon disulphide. The resultant *p-methoxyphenyl 1 : 1-diphenylethyl ketone* (5·8 g., 64%) was sparingly soluble in ethyl alcohol, from which it crystallised in feathery needles, m. p. 136° (Found: C, 83·7; H, 6·6. $C_{22}H_{20}O_2$ requires C, 83·5; H, 6·4%).

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416. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part III. A Kinetic Investigation of the Alkylation of Benzene by Pivaloyl Chloride.*

By EUGENE ROTHSTEIN and ROWLAND W. SAVILLE.

The kinetics of the reaction between pivaloyl chloride and benzene in the presence of aluminium chloride has been investigated. There is a straight-line relation between time and the logarithm of the concentration of the acid chloride, and the first-order constant deduced therefrom is independent of the concentrations of both the halide and the hydrocarbon but varies with the square of that of the aluminium chloride. Thus the rate-determining stage of hydrocarbon formation is either that of formation of the complex between pivaloyl chloride and the catalyst or of the decomposition thereof. These observations are contrasted with those of Olivier (references below) for the acylation of benzene with benzoyl chloride and of Ulich and Heyne for the corresponding alkylation with *n*-propyl chloride. These authors find that in these cases the rates of reaction are dependent on the concentrations of both the benzene and the complex formed by the halide with the catalyst.

THE qualitative results so far recorded throw little light on the factors influencing the alkylation of benzene by *tertiary* acid derivatives. In order to obtain a greater insight into the mechanism of the reaction and in view of the general considerations to be discussed in Part V, some preliminary kinetic investigations have been carried out. The kinetics of the *acylation* of benzene by acyl halides have been studied by Olivier (*Rec. Trav. chim.*, 1914, **33**, 91, 344; 1915, **35**, 109; 1918, **37**, 205), who found that, as a result of complex formation with the ketone, the loss of catalytic efficiency of the aluminium halide influences the velocity of the reaction. This is not the case for alkylation. We have commented on this point already (Part II) and we return to it later.

Alkylation by *alkyl* halides in presence of gallium chloride has been carried out by Ulich and his collaborators (Ulich and Heyne, *Z. Elektrochem.*, 1935, **41**, 509; Ulich and Fragstein, *Ber.*, 1939, **72**, *B*, 291; Ulich, *Z. Elektrochem.*, 1943, **49**, 291) who followed the reaction between propyl chloride and benzene by measuring the hydrogen chloride evolved. In each case these authors considered the initial stage to be the formation of a complex between the acid or alkyl halide and the catalyst:

$$\text{R·COCl} + \text{AlCl}_3 \rightleftharpoons \text{R·COCl,AlCl}_3$$
$$\text{RCl} + \text{GaCl}_3 \rightleftharpoons \text{RCl,GaCl}_3$$

The second stages differ slightly for the reason stated above:

$$\text{R·COCl,AlCl}_3 + \text{C}_6\text{H}_6 \longrightarrow \text{R·COPh,AlCl}_3 + \text{HCl}$$
$$\text{RCl,GaCl}_3 + \text{C}_6\text{H}_6 \longrightarrow \text{Ph·R} + \text{GaCl}_3 + \text{HCl}$$

Olivier calculated his second-order constants for the reaction on the basis of a bimolecular reaction between the complex and benzene, Ulich on the basis of a termolecular reaction in-

volving the concentrations of the catalyst, the alkyl chloride, and benzene. For values not less than that of the halide, changes in the initial concentration of the catalyst were without effect on the rate of reaction. Thus, both the acylation and alkylation reactions were of the second-order, dependent on the concentrations of the halide and of the benzene. It may be remarked that the catalytic efficiency of the gallium chloride decreased with the progress of the reaction and this seems characteristic of our alkylation reactions also, even though in theory the concentration remains constant. It is possibly due to traces of moisture or to some other cause not directly attributable to the reaction studied.

The reaction of pivaloyl chloride differs markedly from those described above. One obvious difference makes it necessary to predicate at least three stages which, without making any new assumptions, can be set down in the following reactions:

$$CMe_3{\cdot}COCl + AlCl_3 \rightleftharpoons \text{Complex 1}$$
$$\text{Complex 1} \longrightarrow \text{Complex 2} + CO$$
$$\text{Complex 2} + C_6H_6 \longrightarrow CPhMe_3 + AlCl_3 + HCl$$

The first of these may be identified with the initial stages of Olivier's and Ulich's reactions. The formation of a complex is well established by inference (Olivier, *loc. cit.*; Rothstein and Saboor, *J.*, 1943, 425), by experiment with radioactive isotopes (Fairbrother, *J.*, 1937, 503), and by actual isolation (Saboor, *J.*, 1945, 922). It is not of course necessarily true that the identical complex is present in each type of reaction. The third equation may provisionally be assumed to correspond with the second of Ulich though only indirect evidence and analogy are available at present. As is evident from the results described later in this paper, the present work concerns the first two stages only, these including any intermediate reaction coming before the final production of hydrocarbon.

In following the kinetics of the condensation, advantage was taken of the possibility of titrating the unchanged acid halide (compare Olivier, *loc. cit.*), thereby eliminating the uncertainties that are inherent when the volume of hydrogen halide is measured. This latter method, first adopted by Steele (*J.*, 1903, 1470) and later with modification by Martin (*J. Amer. Chem. Soc.*, 1935, **57**, 2584) and by Ulich (*loc. cit.*), does not afford very consistent results and for that reason was criticised by Olivier, but obviously the titration method was not applicable to alkylations by alkyl halides.

Apart from other considerations, the use of a titration method necessitates a homogeneous medium, and a search had to be made for a solvent in which the catalyst would remain in solution when it was mixed with the other reactants. Nitromethane was found to be excellent in many respects, but decomposition occurred in certain cases, and because of its interaction with alkali it would have to be removed completely before the unchanged acid chloride could be titrated. With the concentrations used it was found that a solution of aluminium chloride in nitrobenzene fulfilled the requirements mentioned above, a constant concentration of it being used throughout the determinations. The possibility of following the reaction by the quantitative absorption of the evolved carbon monoxide was considered, but the difficulties arising from varying pressures and from the absence of reagents for absorbing the gas suitably for accurate work made it desirable to employ an alternative method.

The quantities of the various reagents used were very similar to those used by Ulich and Heyne, though these authors provide very scanty details of their experiments. Therefore conclusions based on our work are comparable with theirs. Except in one case (experiment 10), the concentration of the catalyst was less than that of the acid chloride, and a straight line relation between the logarithm of the concentration of the latter and the time was observed. There was a short period at the beginning of most of the runs (nos. 1, 2, 3, 5, 6, and 9) when the concentration changed rather rapidly, but this covered only a small portion of the curve which rapidly straightened out. Table I summarizes the results obtained. Nitrobenzene (20 ml.) was present in every case, the concentration being 1·08 g.-mols./l.

From Table I it is evident that up to concentrations of 0·13 g.-mol./l. of aluminium chloride, the reaction gives a first-order constant which is not affected by changes in the initial concentrations of the acid chloride (compare expts. nos. 1 and 5), nor by the presence or absence of benzene (expts. nos. 5 and 8). On the other hand, the velocity constant is proportional to the square of the concentration of the catalyst; there is a straight-line relation between the two quantities, the curve being displaced somewhat along the axis of the velocity constant. The latter can be fairly accurately calculated from the equation, $k_1^{20} = 0{\cdot}43 \times [AlCl_3]^2 + 0{\cdot}0002$, which would imply that in the absence of catalyst there is a small residual velocity. This is not

the case however (see Part II). The decrease in the value of the velocity constant when the medium is changed to carbon disulphide is in accordance with the commonly observed experimental fact that a change of solvent affects the speed of the Friedel–Crafts reaction.

TABLE I.

The reaction between pivaloyl chloride and benzene.

Expt.	Concn. of: $AlCl_3$	Concn. of: $CMe_3 \cdot COCl$	G.-mols./l. of benzene	Solvent	$10^3 \times k_1^{20}$	$k_1^{20}/[AlCl_3]^2$
1	0·063	0·630	Solvent	Benzene	0·184	0·46
2	0·063	0·630	,,	,,	0·187	0·47
3	0·063	0·630	,,	,,	0·189	0·48
4	0·127	0·630	,,	,,	0·719	0·45
5	0·063	0·315	,,	,,	0·186	0·47
6	0·087	0·318	,,	,,	0·342	0·45
7	0·063	0·319	0·0	CS_2	0·149	—
8	0·063	0·315	0·315	CS_2	0·151	—
9	0·105	0·540	Solvent	Benzene	0·485	0·44
10	0·322	0·315	,,	,,	—	—

The last experiment is the only one attempted where the ratio of the concentration of aluminium chloride to that of the acid chloride is greater than unity. The reaction was extremely rapid, being about 40% completed between the times of mixing and the first titration. Less than 20% of unchanged acid chloride remained after 45 minutes, compared with 40% after 480 minutes in experiment 1 for instance. We do not, however, consider that the circumstance of the acid chloride concentration being rather less than that of the catalyst is of great significance; it is noticeable that some of the curves tend to flatten out towards the time axis at the end of the reaction, *i.e.*, as the relative concentration of the aluminium chloride increases. This is very marked in the tenth determination also. The calculated value for $10^3 \times k_1^{20}$ is about 4·5, which gives 18 seconds as the calculated time for the 39% change which occurs between the first and the second titration, the experimental value being 19 seconds. The validity of this agreement should be qualified because the initial reaction is too rapid for accurate measurement, but it may be noted that the general shape of the curve resembles the earlier curves but is much more convex towards the time axis.

These experiments do not in themselves enable a decision to be made as to which of the first two reactions is rate-determining. It may well be that, whilst at low concentrations of the catalyst the first is the slower, the rate of formation of complex 1 may exceed that of its decomposition to complex 2 as the concentrations of catalyst are increased. It is convenient to defer to later papers any further discussion on this point and on the role of the aluminium chloride for which there is not yet sufficient evidence.

EXPERIMENTAL.

Preparation of Starting Materials.—Pivalic acid, prepared from pure pinacol hydrate (*Org. Synth.*, Coll. Vol. 1, 459, 512), was dried by distillation with benzene and fractionated twice, the product having m. p. 34—35° and b. p. 77—78°/20 mm. Freshly distilled, purified thionyl chloride was used for preparing the acid chloride. This after careful fractionation had b. p. 104—107°, and was then fractionally distilled using an electrically heated column, packed with glass helices. A very high initial reflux ratio was used, otherwise dissolved hydrogen chloride tended to carry over a considerable amount of the acid chloride below its true boiling point. The pivaloyl chloride (b. p. 106·5°) was stored in a glass-stoppered flask over phosphoric oxide.

The benzene (B.D.H. sulphur-free, of "molecular-weight quality") was dried (Na) and distilled. The carbon disulphide and the nitrobenzene were of AnalaR standard and were purified and distilled.

The catalyst was prepared by passing dry hydrogen chloride over pure aluminium foil at a dull red heat, and was then resublimed in a current of the same gas. The aluminium chloride, practically white, was stored over phosphoric oxide in a desiccator. It was resublimed immediately before use, otherwise the small lumps made dissolution in nitrobenzene difficult.

Calibration Curve for Pivaloyl Chloride.—2N-Aqueous sodium hydroxide (20 ml.) was pipetted into each of four 100-ml. stoppered flasks. Various quantities of pure pivaloyl chloride were weighed into each flask from a weight-burette, and set aside overnight. The hydrolyses were then completed by heating the liquids under reflux for 1 hour on the steam-bath. After cooling and acidification with dilute hydrochloric acid, the liquid was extracted six times with ether. Each of the extracts was washed with a little water, the aqueous layer being returned to the main bulk, and the extraction continued. The ethereal layers were united, the solvent was removed by distillation, and the residue dissolved in 95% alcohol (50 ml.). Titration with sodium hydroxide (0·102N.) with phenolphthalein as indicator gave the results shown in Table II (the alcohol gave a blank titration of 0·2 ml. which was subtracted from the main titration, the corrected figures being shown in the table).

TABLE II.

Calibration curve for titrations of pivaloyl chloride.

G. of acid chloride taken	0·1271	0·2880	0·5101	0·7759
Ml. of NaOH required	10·3	22·8	40·7	61·0

The two quantities, when plotted, gave a straight-line graph, the weight of pivaloyl chloride at each point corresponding to 97·2% of the actual weight taken. Identical results were obtained by repeating the calibration in the presence of small amounts of nitrobenzene and of the reaction product, namely *tert.*-butylbenzene.

Preliminary Measurements.—Since certain Friedel–Crafts reactions may occur without the use of aluminium chloride, it was necessary to ascertain that no uncatalysed reaction took place under the conditions of the experiment. Pure pivaloyl chloride (1·880 g.) was weighed into pure dry benzene, and the solution made up to 50 ml. in a thermostat at 20°. At intervals, 10-ml. samples were withdrawn and the weight of acid chloride determined. The results are shown in Table III.

TABLE III.

Reaction of pivaloyl chloride with benzene in absence of catalyst.

Time (minutes)	0	450	1220
Pivaloyl chloride (g.-mol./l.)	0·3120	0·3119	0·3114

Similar experiments with solutions containing small quantities of nitrobenzene and *tert.*-butylbenzene showed the virtual absence of uncatalysed reaction over the normal experimental period.

Determination of Velocity Constants.—The reaction vessel was a three-neck flask fitted with a mercury-sealed stirrer and an inlet tube for dry nitrogen. The third neck was normally closed by a calcium chloride guard-tube and was used for withdrawing the samples. The vessel was immersed in a thermostat at 20°. The reaction vessel and all the flasks used were dried at 110° and kept in a large desiccator.

A solution of the pure, freshly distilled acid chloride in the solvent was made up in a graduated flask, the volume of liquid being adjusted with the flask immersed in the thermostat. A solution of freshly sublimed aluminium chloride in nitrobenzene was similarly prepared. The concentration of nitrobenzene was maintained constant throughout the determinations. The catalyst solution was added to a measured volume of the solvent in the reaction vessel and, when it had reached the temperature of the bath, that of the acid chloride was added. A slow stream of nitrogen was passed through the apparatus during the determination. After reaction had begun, 10-ml. samples were withdrawn at suitable intervals, using pipettes fitted with drying tubes, and run directly into sodium hydroxide (20 ml.), the pivalic acid being determined by the standardised method. The process was modified somewhat when high concentrations of the catalyst were used. In this case it was added directly to the reaction flask containing the nitrobenzene and stirred until dissolution was complete.

Results.—For the first three experiments, benzene was used as solvent, the concentrations of the acid chloride and the aluminium chloride being 0·630 and 0·063 g.-mol./l., respectively. The figures obtained are given in Table IV. The values of $10^3 \times k_1^{20}$ were obtained by plotting the curves and reading off the slope.

TABLE IV.

Time (min.)	NaOH (ml.)	CMe_3·COCl (g.)	CMe_3·COCl (g.-mol./l.)	$\log_{10}$ [CMe_3·COCl]	Time (min.)	NaOH (ml.)	CMe_3·COCl (g.)	CMe_3·COCl (g.-mol./l.)	$\log_{10}$ [CMe_3·COCl]
Experiment 1.									
0	57·4	0·730	0·605	Ī·782	154	40·7	0·510	0·424	Ī·627
13·7	52·4	0·665	0·552	Ī·742	237	33·9	0·430	0·357	Ī·553
48·7	48·8	0·618	0·513	Ī·710	336	28·7	0·365	0·302	Ī·480
89·5	46·0	0·584	0·484	Ī·685	524	22·7	0·288	0·239	Ī·378
				$10^3 \times k_1^{20} = 0·184.$					
Experiment 2.									
0	59·1	0·750	0·622	Ī·794	197	38·1	0·484	0·402	Ī·604
19·3	56·1	0·712	0·591	Ī·772	258	34·0	0·430	0·357	Ī·553
72·6	48·9	0·618	0·513	Ī·710	338	30·1	0·380	0·315	Ī·498
118	44·1	0·562	0·466	Ī·668	447	25·6	0·325	0·270	Ī·431
				$10^3 \times k_1^{20} = 0·187$					
Experiment 3.									
0	58·8	0·747	0·619	Ī·792	266	34·1	0·432	0·358	Ī·554
60	50·4	0·642	0·532	Ī·726	364	82·0	0·355	0·294	Ī·468
141	42·4	0·538	0·446	Ī·649	463	24·1	0·305	0·253	Ī·403
				$10^3 \times k_1^{20} = 0·189.$					

Table V shows the effect of doubling the concentration of the catalyst (experiment 4), of halving the concentration of the acid chloride (experiment 5), and of halving the concentration of acid chloride and increasing that of aluminium chloride (experiment 6).

TABLE V.

Time (min.)	NaOH (ml.)	CMe_2·COCl (g.)	CMe_2·COCl (g.-mol./l.)	Log_{10} [CMe_2·COCl]	Time (min.)	NaOH (ml.)	CMe_2·COCl (g.)	CMe_2·COCl (g.-mol./l.)	Log_{10} [CMe_2·COCl]
Experiment 4: [CMe_2·COCl] = 0·630 g.-mol./l.; [$AlCl_3$] = 0·127 g.-mol./l.									
0	55·0	0·700	0·581	$\bar{1}$·764	167	16·0	0·202	0·168	$\bar{1}$·225
16·5	49·1	0·623	0·517	$\bar{1}$·713	239	10·3	0·127	0·105	$\bar{1}$·021
46·5	38·5	0·489	0·406	$\bar{1}$·608	327	6·5	0·082	0·068	$\bar{2}$·832
82·2	29·2	0·370	0·307	$\bar{1}$·485					
$10^3 \times k_1^{20} = 0·719$.									
Experiment 5: [CMe_2·COCl] = 0·315 g.-mol./l.; [$AlCl_3$] = 0·063 g.-mol./l.									
0	30·0	0·380	0·315	$\bar{1}$·499	224	19·2	0·243	0·202	$\bar{1}$·305
31	28·1	0·356	0·295	$\bar{1}$·470	293	16·7	0·210	0·174	$\bar{1}$·241
78·5	25·3	0·324	0·269	$\bar{1}$·430	364	14·2	0·179	0·149	$\bar{1}$·172
156	22·0	0·279	0·232	$\bar{1}$·365	480	12·6	0·159	0·132	$\bar{1}$·120
$10^3 \times k_1^{20} = 0·186$.									
Experiment 6: [CMe_2·COCl] = 0·318 g.-mol./l.; [$AlCl_3$] = 0·087 g.-mol./l.									
0	30·3	0·384	0·319	$\bar{1}$·503	191	15·1	0·192	0·159	$\bar{1}$·202
21·5	27·0	0·342	0·284	$\bar{1}$·453	218	13·7	0·172	0·143	$\bar{1}$·155
83·5	21·3	0·270	0·224	$\bar{1}$·351	288	10·8	0·136	0·113	$\bar{1}$·053
128	17·4	0·223	0·185	$\bar{1}$·267	317	9·7	0·121	0·100	$\bar{1}$·002
$10^3 \times k_1^{20} = 0·342$.									

The determinations shown in Table VI were carried out in carbon disulphide. They show the effect of varying the hydrocarbon concentration; that of aluminium chloride was 0·063 g.-mol./l. in both cases.

TABLE VI.

Time (min.)	NaOH (ml.)	CMe_2·COCl (g.)	CMe_2·COCl (g.-mol./l.)	Log_{10} [CMe_2·COCl]	Time (min.)	NaOH (ml.)	CMe_2·COCl (g.)	CMe_2·COCl (g.-mol./l.)	Log_{10} [CMe_2·COCl]
Experiment 7: [CMe_2·COCl] = 0·319 g.-mol./l.; [benzene] = zero.									
0	30·7	0·386	0·320	$\bar{1}$·505	248	21·2	0·270	0·224	$\bar{1}$·350
28·5	28·0	0·355	0·295	$\bar{1}$·470	316	19·7	0·242	0·201	$\bar{1}$·303
72	27·6	0·350	0·290	$\bar{1}$·462	391	17·2	0·217	0·180	$\bar{1}$·256
112	26·0	0·330	0·274	$\bar{1}$·438	455	14·9	0·189	0·157	$\bar{1}$·196
$10^3 \times k_1^{20} = 0·149$.									
Experiment 8: [CMe_2·COCl] = 0·315 g.-mol./l.; [benzene] = 0·315 g.-mol./l.									
0	30·8	0·387	0·321	$\bar{1}$·506	220	21·7	0·274	0·227	$\bar{1}$·356
49	28·7	0·364	0·302	$\bar{1}$·480	330	18·8	0·239	0·198	$\bar{1}$·297
130	25·2	0·318	0·264	$\bar{1}$·422	400	16·8	0·212	0·176	$\bar{1}$·245
$10^3 \times k_1^{20} = 0·151$.									

The last two determinations, Table VII, were carried out in benzene and again showed the effects of large increases in the catalyst concentration. The curve for experiment 10 does not fit any simple expression for the velocity constant.

TABLE VII.

Time (min.)	NaOH (ml.)	CMe_2·COCl (g.)	CMe_2·COCl (g.-mol./l.)	Log_{10} [CMe_2·COCl]	Time (min.)	NaOH (ml.)	CMe_2·COCl (g.)	CMe_2·COCl (g.-mol./l.)	Log_{10} [CMe_2·COCl]
Experiment 9: [CMe_2·COCl] = 0·540 g.-mol./l.; [$AlCl_3$] = 0·105 g.-mol./l.									
0	50·8	0·648	0·537	$\bar{1}$·730	142	23·1	0·294	0·244	$\bar{1}$·388
20	43·5	0·554	0·460	$\bar{1}$·663	216	13·4	0·171	0·142	$\bar{1}$·153
81·5	30·9	0·394	0·327	$\bar{1}$·514	310	10·2	0·130	0·108	$\bar{1}$·034
$10^3 \times k_1^{20} = 0·485$.									
Experiment 10: [CMe_2·COCl] = 0·315 g.-mol./l.; [$AlCl_3$] = 0·322 g.-mol./l.									
0	15·1	0·192	0·159	$\bar{1}$·201	77	4·3	0·054	0·044	$\bar{2}$·643
3	10·6	0·135	0·112	$\bar{1}$·049	127	4·2	0·052	0·042	$\bar{2}$·623
18	6·1	0·076	0·063	$\bar{2}$·801	200	3·5	0·045	0·037	$\bar{2}$·568
45	4·4	0·055	0·046	$\bar{2}$·663					

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417. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part IV. Preliminary Kinetic Data on the Acylation of Aromatic Compounds by Pivaloyl Chloride.*

By Eugene Rothstein and Rowland W. Saville.

The acylation of aromatic compounds by tertiary acid halides in presence of aluminium chloride as a catalyst is simultaneous with alkylation, and no simple order for the rate of the reaction between pivaloyl chloride and anisole has been found. Analysis of the kinetic values is the more difficult because of complex formation between aluminium chloride and the ketonic product which causes loss of catalytic efficiency, this affecting differently the rates of alkylation and acylation. There is reason for believing that, when the concentration of the catalyst drops below 0·025 g.-mol./l., the rate of acylation is negligibly small, so that only alkylation occurs after this point. Under the conditions used, graphic representation of the results indicates that only alkylation occurs when toluene is substituted for anisole. The times measured for 10% and 25% change under identical conditions using benzene, toluene, and anisole, respectively, as the aromatic components are greatest for anisole, and it can therefore be tentatively assumed that the rate-determining step for the above reactions is that of complex formation between the catalyst and acid halide.

A kinetic study of the simultaneous alkylation and acylation of aromatic compounds, such as very often occur when *tertiary* acids and their derivatives are used, presents particular difficulties because the concentration of the catalyst, which remains approximately constant for alkylation, is effectively reduced when a ketone is produced owing to the formation of a stable complex with the product. The added difficulty that the velocity constant for alkylation is proportional to the square of the concentration of the catalyst necessitates accurate determination of all the products formed during the reaction. In his papers on the acylation of benzene with benzoyl halides, Olivier (for references see preceding paper) showed that in an *excess* of hydrocarbon a first-order reaction occurred, the rate of which was independent of the initial concentration of the acid halide but not of that of the catalyst. Owing to the formation of a complex with the ketone, referred to above, only one molecule of the acid chloride was transformed by the aluminium chloride, this being true when a limited quantity of benzene in carbon disulphide solution was used. In the latter case, the rate was proportional to the concentrations of both the acid halide (or the acid halide–catalyst complex) and the hydrocarbon, *i.e.*, a second-order constant was obtained, and there was some evidence that a constant proportional to the square of that of the benzene fitted the data. With regard to the aluminium chloride or bromide, Olivier found that the first-order velocity constant was multiplied by 1·3 when the initial catalyst concentration was doubled.

It has not yet been found possible to carry out complete kinetic analyses and indeed at present we do not require them. The results so far obtained have, however, made it possible to make certain tentative deductions. Before considering the actual determinations reference should be made to the influence, on alkylation, of formation of the complex between the catalyst and ketone because it could not be assumed *a priori* that this would be associated with loss of catalytic efficiency as in the case of acylation (Part III, preceding paper; Olivier, *loc. cit.*). Inspection of the kinetic results might well be considered to indicate the contrary. A qualitative test has been performed by adding an excess of pivaloyl chloride to a solution of methoxyphenyl *tert.*-butyl ketone in benzene containing about two-thirds of a mole of aluminium chloride per mole of ketone. There was no visible reaction until the concentration of aluminium chloride was raised to that of the ketone. It was therefore concluded that uncombined aluminium chloride is essential for alkylation, as for acylation.

The relevance of the foregoing is seen in the curves obtained when pivaloyl chloride is condensed with anisole, the proportions of the reactants being shown in Table I.

In each case there was an initial rapid reaction, followed by a slow one, which appeared as a straight-line relation between the logarithm of the acid chloride concentration and the time, the slope being nearly identical for the three experiments. The general appearance of the curves is similar to those described in Part III, but the steep curved portions are much longer in the present instances. If from the qualitative experiment outlined earlier in the paper it is assumed that no reaction would take place if *all* the catalyst had been used in forming the ketone–catalyst complex, it would seem reasonable to suppose that acylation ceases when the aluminium chloride has reached a certain minimum figure, in this case approximately 0·025 g.-mol./l. Experiment " B " was repeated at the boiling point (in order to ensure complete reaction) using

identical concentrations. The yield of ketone actually isolated was 20% (based on the acid chloride), corresponding to nearly 62% of the original aluminium chloride.

TABLE I.

Friedel–Crafts condensation of pivaloyl chloride with anisole.

Experiment:	"B."	"C."	"D."
Initial $[AlCl_3]$ (g.-mol./l.)	0·063	0·063	0·064
$[CMe_3{\cdot}COCl]$ (g.-mol./l.)	0·314	0·315	0·063
[Anisole] (g.-mol./l.)	solvent	0·315	0·063
Reaction medium	anisole	CS_2	CS_2
$10^3 \times k_1^{20}$ *	0·046	0·042	0·051
Final $[AlCl_3]$ † (calc.) (g.-mol./l.)	0·025	0·022	0·027

* Calculated from the straight (middle) portion of the curve. (The curves flatten out slightly towards the end of the reaction.)

† Calculated from: $k_1 = 0{\cdot}43 \times [AlCl_3]^3 + 0{\cdot}0002$.

It may be observed that only when anisole was the solvent did the gram-molecular quantity of acid chloride converted, into what was presumably a mixture of hydrocarbon and ketone, exceed that of the aluminium chloride. Anisole is a medium in which both reactions may be expected to be accelerated and, though with the increase of the rate of ketone formation the amount of hydrocarbon would decrease owing to its dependence on the square of the concentration of the catalyst, nevertheless it is possible that, initially, relatively large amounts may be formed.

Ketone formation can thus be recognised by the type of curve obtained when the logarithm of the concentration of the acid chloride is plotted against time; a straight line would indicate its absence. It was mentioned in Part II (this vol., p. 1950) that very little ketone (less than 7%) was produced when 0·1 mol. of aluminium chloride was used with toluene; reduction of the catalyst concentration to 0·063 g.-mol./l. should lower that of the ketone to negligibly small proportions. This was reflected in the results obtained for toluene, which afforded a figure for $10^3 \times k_1^{20}$ (0·153) practically identical with that for benzene (0·151) measured under the same conditions.

In conclusion, we found that the overall rates for the various reactions, judged by the rate of disappearance of the acid chloride, are not very different from one another when the initial concentrations of the various components of the reactions are identical. This is shown in Table II.

TABLE II.

Time for 10% and 25% change in carbon disulphide solution.

$[AlCl_3]$ = 0·063 g.-mol./l.; [Aromatic compound] = $[CMe_3{\cdot}COCl]$ = 0·314 g.-mol./l.

Aromatic compound:	Benzene.	Toluene.	Anisole.
Time for 10% change (mins.)	50	43	98
Time for 25% change (mins.)	200	200	530

These figures appear to indicate that the rate-determining stage for the reaction may be the formation of the first complex (Part III) but the complexity of the kinetics of the two competitive reactions makes it preferable to treat such a deduction with reserve.

EXPERIMENTAL.

Qualitative Experiments.—Reaction between pivaloyl chloride and benzene in the presence of methoxyphenyl tert.*-butyl ketone.* Pivaloyl chloride (10 g., 0·079 mols.) in benzene (10 c.c.) was added to a stirred mixture of aluminium chloride (6 g., 0·045 mol.), methoxyphenyl *tert.*-butyl ketone (11·7 g., 0·061 mol.), and benzene (80 c.c.). There was no visible reaction at room temperature, and no gases were evolved even after several hours. When the mixture was heated to the b. p. there appeared to be an exceedingly slow reaction, the volume of the gases being hardly more than that required by the expansion of the air within the reaction vessel. The mixture was now cooled to room temperature, and a further quantity (3 g.) of aluminium chloride added such that there was now a very slight excess (0·006 mol.) compared with the ketone. The mixed gases (hydrogen chloride and carbon monoxide) were now liberated at *ca.* 100 c.c. per hour. A further addition of the catalyst (3 g.) immediately accelerated the reaction, and within a minute the whole of the carbon monoxide was eliminated, the total volume of gases collected being >2 l.

Reaction between pivaloyl chloride and anisole in the presence of low concentrations of aluminium chloride (cf. *determination* C). The acid chloride (3·4 g.), anisole (3 g.), aluminium chloride (0·8 g.), nitrobenzene (8 c.c.), and carbon disulphide (75 c.c.) were heated to the b. p., and the carbon monoxide collected for identification, but no attempt was made to measure its volume. Approx. 1·1 g. (20%) of *p*-methoxyphenyl *tert.*-butyl ketone, b. p. 160°/18 mm., was isolated and identified by its semicarbazone, m. p. 150—151° (Part II).

Kinetic Determinations.—The method used was that described in Part III. The aluminium chloride (initial concentration, 0·063 g.-mol./l., in every case except the last) was dissolved in nitrobenzene (20 ml.) before addition to the reaction mixture.

Time (min).	NaOH (ml.).	CMe_3·COCl (g.).	CMe_3·COCl (g.-mol./l.).	Log_{10} [CMe_3·COCl].
Experiment " A." Initial concns.: toluene, 0·314 g.-mol./l.; pivaloyl chloride, 0·314 g.-mol./l. Solvent: carbon disulphide.				
0	29·5	0·373	0·308	$\bar{1}$·489
43	27·1	0·343	0·286	$\bar{1}$·456
201	22·0	0·279	0·232	$\bar{1}$·366
290	18·5	0·236	0·195	$\bar{1}$·291
511	13·6	0·171	0·141	$\bar{1}$·150
675	10·8	0·136	0·113	1·052

$10^2 \times k_1^{20} = 0·153.$

The following table describes three condensations with anisole, the first with the anisole as solvent, the other two in carbon disulphide,

Time (min.).	NaOH (ml.).	CMe_3·COCl (g.).	CMe_3·COCl (g.-mol./l.).	Log_{10} [CMe_3·COCl].
Experiment " B." Initial concns.: anisole, solvent; pivaloyl chloride, 0·314 g.-mol./l.				
0	22·9	0·290	0·240	$\bar{1}$·380
72	20·4	0·257	0·213	$\bar{1}$·329
183	18·2	0·230	0·192	$\bar{1}$·283
304	17·2	0·221	0·183	$\bar{1}$·263
416	16·6	0·209	0·173	$\bar{1}$·238
452	16·2	0·204	0·170	$\bar{1}$·230
Experiment " C." Initial concns.: anisole, 0·315 g.-mol./l.; pivaloyl chloride, 0·315 g.-mol./l. Solvent: carbon disulphide.				
0	30·0	0·380	0·315	$\bar{1}$·498
98	27·3	0·346	0·287	$\bar{1}$·458
199	26·9	0·341	0·283	$\bar{1}$·452
319	26·6	0·337	0·280	$\bar{1}$·447
530	26·2	0·333	0·276	$\bar{1}$·440
Experiment " D." Initial concns.: anisole, 0·063 g.-mol./l.; pivaloyl chloride, 0·063 g.-mol./l.; $AlCl_3$, 0·064 g.-mol./l. Solvent: carbon disulphide.				
0	15·3	0·195	0·064	$\bar{2}$·806
91	12·4	0·157	0·052	$\bar{2}$·719
247	10·4	0·133	0·044	$\bar{2}$·647
358	9·5	0·121	0·040	$\bar{2}$·606
551	9·0	0·115	0·038	$\bar{2}$·580

THE UNIVERSITY, LEEDS. [*Received, January 27th,* 1949.]

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418. *The Reaction between Aromatic Compounds and Derivatives of Tertiary Acids. Part V. The Stability of the Carbonyl Group in Certain Acid Halides and Anhydrides.*

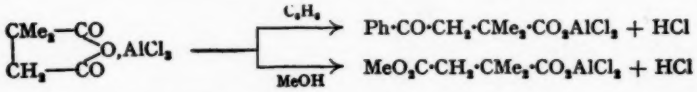
By EUGENE ROTHSTEIN and ROWLAND W. SAVILLE.

The factors influencing the acylation or alkylation of aromatic compounds by derivatives of acids in the Friedel–Crafts synthesis are discussed. It is suggested that the stability of the acyl cation $CR_3 \cdot \overset{\oplus}{C}O$ determines the relative rates of the two processes. Loss of carbon monoxide results in the formation of an electrophilic carbonium ion, $R_3C^{\oplus}$, which can be substituted in the nucleus, yield an olefin, or undergo rearrangement. The effect of substituents on the relative ease of elimination of carbon monoxide is also examined and it is shown that the decomposition may be used for the determination of the course of the reaction. Thus condensation of diarylacetyl chlorides with benzene is attended by the simultaneous liberation of this gas; this was not detected by previous workers in this field and in consequence an explanation advanced by McKenzie, Roger, and McKay (*J.*, 1932, 2597) of the formation of diphenyl- and triphenyl-methane from phenyl-*p*-tolylacetyl chloride is untenable. These diarylacetic acid derivatives provide the first instance of an unstable *secondary* acyl ion, $Ar_2CH \cdot \overset{\oplus}{C}O$.

THE experiments described in the foregoing papers enable the discussion of the hypotheses outlined by one of us and Saboor (*J.*, 1943, 425; see also Saboor, *J.*, 1945, 922) to be elaborated.

We now wish to restate the portion dealing with the Friedel–Crafts reactions of *tertiary* acid derivatives so as to include the new results, making the incidental modifications, foreshadowed in Part I, necessitated by the replacement of the acid anhydride by the chloride. Rothstein and Saboor made no attempt to distinguish between the intermediate stages that must intervene before the final products are formed, and it is essential to what follows in the latter part of this paper to extend the comments we made in Part III on this question.

The formation of a complex which may be written $R\cdot\overset{\oplus}{C}O$, $[AlCl_4]^{\ominus}$ has already been mentioned as constituting the initial reaction in the synthesis of ketones from acid chlorides, and Saboor (*loc. cit.*) isolated a product of this kind from *as*-dimethylsuccinic anhydride which decomposed in the expected manner when the appropriate reagents were added:



Notwithstanding the differences between the reactions of acid halides and anhydrides it seems reasonable to assume that the reactions are equivalent in the first stage for both classes of compounds. On the other hand, because of the dependence of the velocity constant on the square of the catalyst concentration we cannot be sure that the intermediate involved in alkylation is precisely the same as in acylation. They *may* be identical but, if they are not, then the two must be in equilibrium with one another since variation in the aromatic component alters the ratio of hydrocarbon to ketone (Part II). Olivier (*Rec. Trav. chim.*, 1914, **33**, 91) did in fact suggest that the initial complex reacted only slowly, but that a second and more reactive complex was formed when the concentration of the catalyst was increased. Modifying his structures somewhat to suit our present symbolism, these were:

$$O{=}CRCl + AlCl_3 \rightleftharpoons \overset{\curvearrowleft}{O{=}}\overset{\oplus}{C}R{-}[\overset{\ominus}{A}lCl_4] \rightleftharpoons \overset{\ominus}{A}lCl_3O{-}\overset{\oplus}{C}\overset{\ominus}{R}{-}[\overset{\ominus}{A}lCl_4]$$

but it must be emphasized that this explanation requires the use of an excess of aluminium chloride and is not altogether applicable to our own experiments where reaction occurs rapidly in the presence of quite low concentrations thereof. Although the first complex might be expected to eliminate carbon monoxide, it is difficult to accept this for the second.

It is generally agreed that the formation of a ketone is the consequence of the electrophilic attack by the positive ion, $R\cdot\overset{\oplus}{C}O$ on the aromatic molecule, no different from, say, bromination or nitration:

$$R\cdot\overset{\oplus}{C}O + H\cdot Ph \longrightarrow R\cdot CO\cdot Ph + \overset{\oplus}{H}$$

the function of the catalyst being to enhance the polarisation of the acid derivative. This mechanism is, however, inadequate in certain respects for Mentzner and Xuong (*Bull. Soc. chim.*, 1947, [iv], **14**, 885) have shown that diarylation can take place using aryl ethers, the suggested formulation being:

$$CHR_2\cdot CO\cdot Cl + ArH \longrightarrow CHR_2\cdot CArCl\cdot OH \longrightarrow CR_2{:}CAr\cdot OH \xrightarrow{ArH} CR_2Ar_2 + H_2O$$
$$[R = Alk\cdot O\cdot C_6H_4{-}]$$

Rothstein and Saboor (*loc. cit.*) suggested a course of reaction (" B ") which in effect is somewhat similar, namely a transition complex, the structures of which when applied to acid halides could be written:

$$H{-}\overset{\curvearrowleft}{C}{-}\overset{\oplus}{C}{=}O\ (AlCl_4)^{\ominus} \qquad \overset{\oplus}{H}\ C{=}C{=}O\ (AlCl_4)^{\ominus}\ \text{etc.}$$

Mentzner and Xuong showed that this reaction only occurred during the original condensation; no diaryl compound resulted from heating the *ketone*, $CHR_2\cdot CO\cdot Ar$ with an ether and aluminium chloride. They ignored the function of the latter, and at present there is very little experimental work to support the above mechanism.

Turning now to alkylation, at least two stages can be distinguished. The first involves the elimination of carbon monoxide and, whether this is a composite reaction or not, it leads to the formation of a carbonium ion:

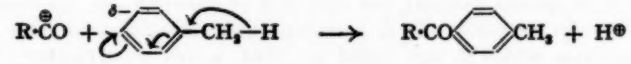
$$R\cdot\overset{\oplus}{C}O[AlCl_4]^{\ominus} \longrightarrow \overset{\oplus}{R} + [AlCl_4]^{\ominus} + CO$$

It is evident that this can take place in the complete absence of an aromatic compound or, alternatively, when the formation of ketone is the slower reaction. With very few exceptions, reference to which is made towards the end of this paper, these decompositions are exhibited exclusively by derivatives of *tertiary* acids; moreover, they occur independently of any subsequent transformation of the carbonium ion. This emerges from the kinetics of the reaction (Part III) and it may be recalled that, when ketone synthesis is absent or virtually so, the concentration of the aromatic component is without effect on the rate-determining stage of the reaction which in consequence must depend solely on the nature of the group R.

The reaction which succeeds the formation of the carbonium complex may follow alternative paths. When a suitable aromatic compound is present, a reaction analogous to ketone formation results, *i.e.*, there is an electrophilic attack by a cation, in this case the carbonium ion: $\overset{\oplus}{R} + H{\cdot}Ph \longrightarrow R{\cdot}Ph + \overset{\oplus}{H}$. Unless the nucleus is deactivated, as, *e.g.*, in nitrobenzene, this is the usual course and, like the ketonic reaction, is subject to the usual orientation rules for electrophilic substitution though in actual examples the effect of the aluminium chloride in modifying the influence of orienting groups may have to be taken into consideration. It is significant that, since alkylation is dependent on the primary formation of the carbonium ion, further activation of the nucleus, beyond that required for any reaction to take place at all, will not influence the proportion of hydrocarbon derivative obtained. On the contrary, it may reduce it by encouraging ketone production. This by contrast is a bimolecular reaction involving the aromatic reagent, and the presence of electron-releasing groups on the latter will facilitate it. There is of course the incidental effect, to which attention has already been directed (Part IV), of the reduction of the activity of the aluminium chloride arising from its combination with the product. Thus the velocities of the two reactions are altered in favour of ketone formation. A modification of this last statement must be applied to the case of alkylation by acid anhydrides because this entails salt formation which again renders the catalyst inactive:

$$(R{\cdot}CO)_2\overset{\oplus}{O}{:}[AlCl_3]^{\ominus} \longrightarrow R{\cdot}\overset{\oplus}{C}O + AlCl_2{\cdot}O{\cdot}COR$$

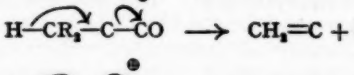
Before leaving the subject of orientation, it is relevant to notice the influence of alkyl groups as set down in Table II of Part II. The high yields of ketone obtained from toluene and ethylbenzene are reduced to 26% for *tert.*-butylbenzene, when the hydrocarbons themselves are the solvents, and to zero in carbon disulphide solution (Table III, *loc. cit.*). This would appear to be the effect of hyperconjugation involving the methyl and ethyl groups, first postulated by Baker and Nathan (*J.*, 1935, 1844), which reverses the normal inductive effect ($Bu^t > Et > Me$). It agrees with our opinion of the validity of the usual orientation rules:

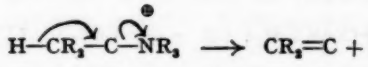


When an aromatic hydrocarbon is not present, a rearrangement of the carbonium ion may occur, *e.g.*, the formation of an olefin:

$$H{-}CR_2{-}\overset{\oplus}{C}\,[AlCl_4]^{\ominus} \longrightarrow CR_2{=}C + H^{\oplus} + Cl^{\ominus} + AlCl_3$$

This of course is the well known mechanism for olefinic decomposition, and written in a slightly different form is another example of this, corresponding to the reaction of quaternary ammonium salts (cf. Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657):





It is not a necessary condition for this reaction that the carbonium ion should be *tertiary* (although it may be so for its *formation* from an acid derivative). It is manifest that the first of these last three reactions can also represent the formation of an olefin from an alkyl halide, but direct evidence is not yet available that both reactions are identical at this point.

It is clear that the prerequisite for the elimination of carbon monoxide in the compounds

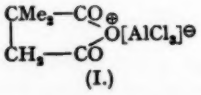
under discussion is the electron-releasing power of the group to which it is attached, that is the stability of the ion $CR_3 \cdot \overset{\oplus}{C}O$. It so happens that when R is alkyl, the decomposition of the ion is comparatively rapid, but if it is halogen the $-I$ effect of the latter reduces the speed considerably, so that *tert.*-butylbenzene is obtained from pivaloyl chloride but trichloroacetyl chloride affords trichloroacetophenone (see below). We find it necessary therefore to modify in certain respects the conclusion reached by Rothstein and Saboor (*loc. cit.*) that *tertiary* acid derivatives never yield ketones and the converse that *primary* and *secondary* ones always do so. It remains generally true for aliphatic acids when the substituent groups are alkyl and for condensations with benzene. The formation of methoxyphenyl *tert.*-butylphenyl ketone demonstrates that it is possible to compensate for the lack of stability of the carbonyl compound by electron accession to the reactive point of the aromatic molecule. On the other hand, an unreactive nucleus does not *as a rule* lead to the expulsion of carbon monoxide in the case of *primary* and *secondary* acids but, as is shown later in this paper, the aryl-substituted acetic acids form an exception.

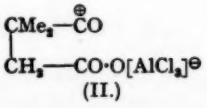
Past work in the Friedel–Crafts reaction provides a number of examples where " anomalous " results have been recorded. The case of oxalyl chloride to which reference was made in Part II is one of a number of instances where a carbonium ion unites with a chlorine atom to yield a chloro-acid chloride (carbonyl chloride) which in the absence of an aromatic compound can be isolated. Dialkylmalonyl chlorides, on the contrary, do not, apparently, form a carbonium ion in spite of their reactions resembling superficially those of oxalyl chloride. The three products obtained are 2 : 2-dialkylindane-1 : 3-dione, dialkyldibenzoylmethane, and dialkylacetophenone, but the last of these products is not the result of elimination of carbon monoxide; we find, in fact, that hardly any of the gas is evolved either in benzene or in carbon disulphide, and the volume is certainly much less than would be expected from the amount of this ketone isolated. It is possible that its presence arises from the decomposition of the β-keto-acid formed by the condensation of one molecule of benzene :

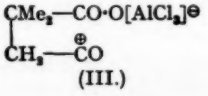
$$ClCO \cdot CR_2 \cdot COCl + HPh \longrightarrow Ph \cdot CO \cdot CR_2 \cdot CO_2H \longrightarrow Ph \cdot CO \cdot CHR_2 + CO_2$$

The di- and tri-chlorocarbonium ions derived from the corresponding acetyl chloride are formed only in the absence of benzene (Böeseken, *Rec. Trav. chim.*, 1910, **29**, 85); otherwise the corresponding ketones result. Hence the acyl ions are comparatively stable. Our own experiments, carried out to determine the amount of carbon monoxide liberated, have furnished only trichloroacetophenone, when anhydrous catalyst was used with trichloro- and tribromoacetyl chloride or trichloroacetic anhydride. Other workers in this field have isolated also triphenylvinyl alcohol.

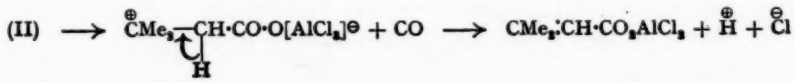
For reasons that will become evident, we were led to examine the reactions of camphoric anhydride with aluminium chloride. It is pertinent to this subject to refer to reactions of dimethylsuccinic anhydride which it was noted (p. 1962) forms a particularly stable complex with the catalyst, the stability probably being due to the resonance energy contributed by structures such as (I), (II), and (III) :


(I.)


(II.)


(III.)

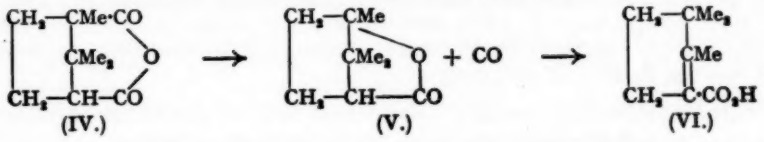
Of these, only (II) can lead to the direct elimination of carbon monoxide; (I) and (III) must revert to the acid. In fact, Desfontaines (*Compt. rend.*, 1902, **134**, 295) obtained a mixture of *as*-dimethylsuccinic and ββ-dimethylacrylic acid. The dimethylacrylic acid is obviously the result of the decomposition of (II) :



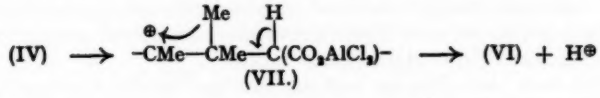
The production of the ketone from benzene suggests that (III) is the predominating structure and that this is a faster reaction than the expulsion of carbon monoxide.

A chloroform solution of camphoric anhydride, similarly treated, affords *iso*lauronolic acid together with certain lactones derived therefrom (Lees and Perkin, *J.*, 1901, **79**, 356; Perkin

and Yates, *ibid.*, p. 1373); it was suggested (*loc. cit.*) that the reaction took place through the intermediate " ψ-campholactone " (α-campholytolactone) (V) :

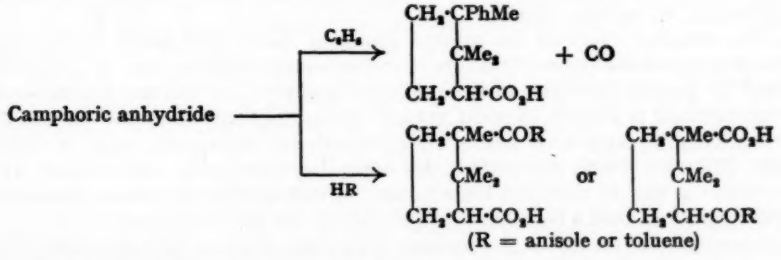


the second stage (V ⟶ VI) was considered to be a pinacolic displacement. The lactone (V) was not isolated in this reaction but was later prepared by a different method and does afford *iso*lauronolic acid (VI), but only by fission of the lactone ring with hydrogen bromide, removal of the bromine with alkali, and finally by an acid isomerisation of the resulting β-campolytic acid (Perkin and Thorpe, *J.*, 1904, **85**, 143). The reaction of campholytolactone with aluminium chloride has not been recorded, but in view of the known reactions of lactones would probably afford (VI). It is clear, however, in the light of the arguments put forward in the preceding pages, that *iso*lauronolic acid is the result of a pinacolic displacement, not of campholytolactone, but of the carbonium ion (VII) derived from the camphoric anhydride :



and we regard, indeed, the rearrangement as a confirmation of our view that a kinetically free carbonium ion is actually formed.

The reaction of camphoric anhydride with benzene is rather unusual in that carbon monoxide is eliminated and 2-phenyl-1 : 1 : 2-trimethyl*cyclo*pentane-5-carboxylic acid is produced (Burcker, *Bull. Soc. chim.*, 1890, [iii], **4**, 112; Burcker and Stabil, *Compt. rend.*, 1894, **119**, 426). Subsequently Eykman (*Chem. Zentr.*, 1907, II, 2046) obtained a ketone by use of toluene or anisole, the position of the acyl group being undetermined :



Most dicarboxylic anhydrides with at least one *non-tertiary* carboxyl group, *e.g.*, *as*-dimethylsuccinic or trimethylsuccinic anhydride, yield ketones with benzene and it would thus appear that the accumulation of methylene and alkyl groups promotes decomposition to such an extent that it is faster than the usually very rapid synthesis of the ketone. Thus the stability of the carbonyl group is rather less than in the trialkylated succinic derivatives but greater than in those of tetramethylsuccinic acid which even with toluene yields only the hydrocarbon. We found it desirable to repeat some of the experiments with camphoric anhydride because the yields of neither the main products nor the carbon monoxide were available. Likewise, in order to complete the comparison with the other alkylated acids, the condensations with *tert.*-butylbenzene (in carbon disulphide) and with acetanilide were carried out. In the former case, 3-p-tert.-*butylphenyl*-1 : 1 : 2-*trimethyl*cyclo*pentane-5-carboxylic acid*, purified by its conversion into the *methyl* ester, was the only product. With acetanilide the condensation is evidently slower than the rearrangement, the reaction affording *iso*lauronolic acid.

It has already been remarked that it is most unusual for a primary or secondary acid halide to produce a hydrocarbon with loss of carbon monoxide, and even when condensation to a ketone cannot take place as with γ-4-methoxy-3-diphenylylbutyryl or β-*p*-nitrophenylpropionyl chloride, the original substance is recovered unchanged (Part I). The ketone was obtained from the acid chlorides of diethylacetic and aceturic acid where it was thought there might be sufficient electron-releasing groups present. It was noticed, however, that, when phenyl-

p-tolylacetyl chloride is condensed with benzene, diphenylmethane alone or with triphenylmethane and triphenylcarbinol is produced according to the purity of the thionyl chloride used for the preparation of the acid chloride (McKenzie and Widdows, *J.*, 1915, **107**, 702; McKenzie, Roger, and McKay, *J.*, 1932, 2597; Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 2049). A possible mechanism, suggested by McKenzie, Roger, and McKay, was one involving three molecules of benzene in the first instance:

$$C_6H_4Me\cdot CHPh\cdot COCl + 3C_6H_6 \longrightarrow H_2O + HCl + C_6H_4Me\cdot CHPh\cdot CHPh_2$$
$$C_6H_4Me\cdot CHPh\cdot CPh_3 \longrightarrow C_6H_4Me\cdot CH_2Ph + CHPh_3$$

In the process the tolyl group was exchanged for phenyl, and the triphenylmethane oxidised to the carbinol. It was presumed that the tetraphenyltolylethane was dissociated into triphenylmethyl and phenyltolylmethyl radicals which then gave the above products.

Now in Part I we described a very similar reaction, in which diphenylethane is obtained from αα-diphenylpropionyl chloride: $CPh_2Me\cdot COCl \longrightarrow CHPh_2Me$, but the above mechanism could not possibly apply in our case because carbon monoxide was evolved in 86% yield. We therefore doubted whether phenyl-*p*-tolylacetyl chloride did actually undergo the transformations suggested. The crucial point was of course the liberation of carbon monoxide which has no place in the proposed scheme. Repetition of the experiment, following the procedure of the three authors, afforded a large volume of carbon monoxide representing a yield of at least 70%. The crystalline products were those previously described, except that a better yield of triphenylcarbinol separated from the reaction mixture.

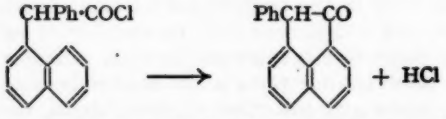
Thus this was the first case that we had encountered where a secondary acid derivative decomposed in this way and the logical deduction is that, whatever be the subsequent changes of the phenyl-*p*-tolylcarbonium ion, the initial step of the reaction is its formation:

$$C_6H_4Me\cdot CHPh\cdot COCl + AlCl_3 \longrightarrow C_6H_4Me\cdot CHPh\cdot \overset{\oplus}{C}O[AlCl_4]^{\ominus} \longrightarrow C_6H_4Me\cdot \overset{\oplus}{C}HPh + CO + \overset{\ominus}{Cl} + AlCl_3$$

To test the matter further, the acid chloride was next condensed with anisole. Ketone should not be formed according to the original mechanism; in fact the substitution of the more reactive aromatic compound might be expected to facilitate complete condensation. Actually, as was expected, very little carbon monoxide was collected and the main product was *methoxyphenyl* α-p-*tolylbenzyl ketone*, m. p. 107—108°.

The electron-releasing effect of the methyl group in the *p*-tolyl group is just sufficient to prevent formation of ketone (where benzene is the solvent); substitution of *p*-tolyl by phenyl is accompanied by partial retention of the carbonyl group. The Friedel–Crafts reaction with diphenylacetyl chloride is known to yield mainly benzoyldiphenylmethane (or the enol form, triphenylvinyl alcohol), triphenyl- and diphenyl-methane (compare, *inter al.* Klingemann, *Annalen*, 1893, **275**, 88; Biltz, *Ber.*, 1899, **32**, 650; Ramart-Lucas, *Ann. Chim.*, 1913, [viii], **30**, 349), but as in the case of the tolyl homologue, the elimination of carbon monoxide was not recorded. We again find that a considerable quantity of the gas is evolved.

The diaryl compounds resemble the tertiary alkylated acids in that cyclisation takes precedence over decomposition. For example, phenyl-α-naphthylacetyl chloride cyclises to 7-phenylacenaphthenone when treated in benzene solution with aluminium chloride (McKenzie and Tattersall, *J.*, 1925, **127**, 2522; Koelsch and Richter, *J. Amer. Chem. Soc.*, 1937, **59**, 2165), and neither the open-chain ketone nor a hydrocarbon is formed:



This is consistent with the conclusion arrived at in Part I that cyclisation occurs preferentially in these cases.

Experimental.

Dialkylmalonyl Chloride Condensations.—(i) *In benzene* (Freund and Fleischer, *Annalen*, 1910, **373**, 291; 1913, **399**, 182). The product from dimethylmalonyl chloride (13·5 g.), aluminium chloride (22 g., 2 mols.), and benzene (140 c.c.) was dibenzoyldimethylmethane (10·5 g., 52%) and a negligible volume of carbon monoxide.

(ii) *In carbon disulphide.* By use of benzene (6·5 g.), dimethylmalonyl chloride (14 g.), and aluminium chloride (23 g., 2 mols.), in carbon disulphide (120 c.c.) solution, there were produced carbon monoxide (37 c.c., 8·1%), phenyl *iso*propyl ketone, b. p. 110—112°/15 mm. (yield, 23%) [identified by its oxime (plates, m. p. 94°, from ligroin) and semicarbazone (needles, m. p. 181°, from ethyl alcohol) (cf. Lapworth

and Steel, *J.*, 1911, **99**, 1885)], dibenzoyldimethylmethane (1·7 g., 8·1%), and a substance (0·5 g.) which crystallised from ligroin in plates, m. p. 99° (0·5 g.) (Found: C, 74·6; H, 5·6. Calc. for $C_{11}H_{10}O_2$: C, 75·8; H, 5·7%) and may have been 2 : 2-dimethylindanedione although repeated crystallisations failed to raise the m. p. to that recorded (103—105°; Gabriel and Neumann, *Ber.*, 1893, **26**, 954).

Similar results were obtained for diethylmalonyl chloride.

Condensations of Chloroacetyl Chlorides with Benzene.—(i) *Chloroacetyl chloride.* Phenacyl chloride (87%) and carbon monoxide (1%), but no benzyl chloride, were formed. (ii) *Dichloroacetyl chloride.* ωω-Dichloroacetophenone (79%) and carbon monoxide (3·6%) were formed. (iii) *Trichloroacetyl chloride.* ωωω-Trichloroacetophenone (56%), carbon monoxide (3·1%), and a tar of high b. p. were produced.

Condensations of Other Halogenated Compounds.—These were carried out in benzene. Trichloroacetic anhydride (Swartz, *Bull. Soc. chim.*, 1895, [iii], **13**, 992; Fichter, Fritsch, and Müller, *Helv. Chim. Acta*, 1923, **6**, 503) afforded carbon monoxide (7%) and trichloroacetophenone (57%); similar results were obtained with trichloroacetyl bromide. α-Bromo*iso*butyryl chloride and bromide gave substantially the products described in the literature, *i.e.*, α-bromo*iso*butyrophenone and 2-methyl-1-indanone.

Condensations of Camphoric Anhydride.—(i) *With benzene.* Aluminium chloride (15 g., 2·1 mols.) was added in small portions to a vigorously stirred solution of the anhydride (10 g.) in benzene (160 c.c.). The volume of carbon monoxide was 1095 c.c. (89%). 2-Phenyl-1 : 1 : 2-trimethyl*cyclo*pentane-5-carboxylic acid crystallised from aqueous alcohol as a powder, m. p. 139° (67%) (Found: C, 77·4; H, 8·6. Calc. for $C_{15}H_{20}O_2$: C, 77·6; H, 8·6%). The diphenyl condensation product (Burcher, *loc. cit.*) was not found, but there was a small quantity of hydrocarbon of undetermined structure which separated from benzene as a crystalline powder, m. p. 80—81° (Found: C, 93·1; H, 6·6%).

(ii) *With anisole.* Substituting anisole for benzene, but otherwise using the same conditions, gave 3·4% of carbon monoxide, and the chief product was 5-(or 2-)anisoyl-1 : 1 : 2-trimethyl*cyclo*pentane-2-(or 5)-carboxylic acid (8 g., 89%), m. p. 165° (from benzene) (Found: C, 70·5; H, 7·5. Calc. for $C_{17}H_{22}O_4$: C, 70·3; H, 7·6%).

(iii) *With toluene.* Conditions were as before. The toluoyl derivative separated from benzene in plates, m. p. 187° (82%). The yield of carbon moxoxide was 3%.

(iv) *With* tert.-*butylbenzene.* A stirred mixture of camphoric anhydride (7 g.), aluminium chloride (10·5 g., 2·1 mols.), and carbon disulphide (70 c.c.) was cooled to 0° and to it was added a solution of *tert.*-butylbenzene (10·5 g., 2 mols.) in carbon disulphide (10 c.c.). There was only slight reaction at this temperature, but after warming there was a vigorous evolution of carbon monoxide (639 c.c., 74·2%). Approx. one quarter of unchanged *tert.*-butylbenzene (2·7 g.) with a rather smaller amount of di-*p*-*tert.*-butylbenzene, in addition to an acid, were obtained. The silver salt of the acid, when boiled with methyl iodide, yielded *methyl* 2-*p*-*tert*-*butylphenyl*-1 : 1 : 2-*trimethyl*cyclo*pentane*-5-*carboxylate*, b. p. 110—115°/0·2 mm. (Found: C, 79·2; H, 9·7. $C_{20}H_{30}O_2$ requires C, 79·5; H, 9·9%).

(v) *With acetanilide.* Aluminium chloride was added in small portions (10 g. in all, 2 mols.) to a chloroform solution of camphoric anhydride (5 g.) and acetanilide (3·6 g.), and the mixture boiled for 1 hour and decomposed with ice. The acid portion was converted into the methyl ester, b. p. 93—95°/17 mm., which appeared to be mainly methyl *iso*lauronolate (Found: C, 70·6; H, 9·7. Calc. for $C_{16}H_{16}O_2$: C, 71·4; H, 9·6%).

Condensations of Diarylacetyl Chlorides.—(i) Phenyl-*p*-tolylacetic acid was prepared from mandelic acid and toluene by the action of anhydrous stannic chloride (McKenzie and Widdows, *loc. cit.*). The recrystallised substance had m. p. 115° (Found: C, 79·8; H, 6·6. Calc. for $C_{15}H_{14}O_2$: C, 79·6; H, 6·2%). A solution of the acid chloride was prepared by warming the acid (22·6 g.) with B.D.H. "redistilled" thionyl chloride (18 c.c.), removing the excess in a vacuum, and dissolving the residue in carbon disulphide (25 c.c.). This was then added to a stirred mixture of aluminium chloride (20 g.). benzene (114 c.c.), and carbon disulphide (31 c.c.) (McKenzie, Roger, and McKay, *loc. cit.*), the evolved gases being collected. The volume of carbon monoxide was approx. 1890 c.c. (70%). The yield of triphenylcarbinol was nearly 33%, more than double that obtained by the above authors. The carbinol was recrystallised from benzene and petrol (b. p. 60—80°) and was identified by comparison (m. p. 159—160°, and mixed m. p.) with an authentic specimen.

(ii) *Diphenylacetyl chloride and benzene.* The acid chloride (prepared from 10·6 g. of acid and excess of thionyl chloride) was dissolved in carbon disulphide (12 c.c.) and added to the stirred mixture of the catalyst (10 g.), carbon disulphide (15 c.c.), and benzene (60 c.c.). The volume of carbon monoxide was 760 c.c. (68%). The oily product on distillation furnished diphenylbenzophenone, b. p. 160°/0·2 mm. which solidified and was recrystallised from light petroleum (b. p. 80—100°). It had m. p. 136° (Found: C, 88·0; H, 5·8. Calc. for $C_{20}H_{14}O$: C, 88·2; H, 5·9%). Yield, 4 g.

(iii) *Phenyl*-p-*tolylacetyl chloride and anisole.* The acid chloride (from 11·3 g. of acid) in carbon disulphide (12 c.c.) was added to aluminium chloride (10 g.), carbon disulphide (15·5 g.), and anisole (50 g.). Scarcely any carbon monoxide was liberated and from the solution was isolated *methoxyphenyl* α-*p*-*tolylbenzyl ketone*, separating from light petroleum (b. p. 80—100°) in colourless needles, m. p. 107—108° (14 g., 88·6%) (Found: C, 83·7; H, 6·5. $C_{22}H_{20}O_2$ requires C, 83·5; H, 6·3%). Fission with alcoholic potash afforded anisic acid, recrystallised from very dilute alcohol to m. p. 184° (Found: C, 63·3; H, 5·4. Calc. for $C_8H_8O_3$: C, 63·2; H, 5·3%).

Condensation of Diethylacetyl Chloride with Benzene.—The acid chloride (5·7 g.), prepared in 72% yield from the acid and thionyl chloride, was mixed with aluminium chloride (11·4 g.) and benzene (60 c.c.). The yields of carbon monoxide and of α-ethylbutyrophenone were 7% and 81%, respectively. The ketone furnished the 2 : 4-*dinitrophenylhydrazone* crystallising from alcohol in needles, m. p. 115—116° (Found: C, 60·2; H, 5·5; N, 15·4. $C_{18}H_{20}O_4N_4$ requires C, 60·5; H, 5·6; N, 15·7%). The oxime (Haller and Bauer, *Compt. rend.*, 1910, **150**, 1477) was unsuitable for the characterisation of the ketone owing to its indefinite m. p.

Condensation of Aceturyl Chloride with Benzene.—This was carried out with aceturyl chloride (9 g.) (Max, *Annalen*, 1909, **369**, 286), aluminium chloride (12 g.), and benzene (60 c.c.), yielding carbon monoxide (8%) and ω-acetamidoacetophenone, crystallising from benzene in feathery plates, m. p.

86—87° (51·5%) (Found: C, 67·5; H, 5·8; N, 7·5. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·2; N, 7·9%). Aceturyl chloride can be obtained in 50% yield by rapidly stirring a mixture of acetylglycine, phosphorus pentachloride, and acetyl chloride cooled to 0° with the usual precautions, and the method affords a convenient synthesis of ω-acetamidoacetophenone. No acetobenzylamide is formed.

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THE UNIVERSITY, LEEDS. [*Received, January 27th*, 1949.]

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419. *Experiments in the Synthesis of Derivatives of α-Aminoacrylic Acid from Serine and N-Substituted Serines.*

By EUGENE ROTHSTEIN.

The condensation of acetamide with pyruvic acid affords αα-diacetamidopropionic acid which eliminates acetamide yielding α-acetamidoacrylic acid (Bergmann and Grafe, *Z. physiol. Chem.*, 1930, **187**, 187). The *methyl* ester, but no other derivative, could be obtained from this acid directly. When treated with alkali under various conditions, *methyl β-chloro-α-acetamidopropionate*, prepared from serine, affords methyl α-acetamido-β-methoxypropionate, *β-chloro-α-acetamidopropionamide*, and *α-acetamidoacrylamide*, as well as methyl acetamidoacrylate. The yields, however, are small and the methods employed are not suitable for preparing these compounds in quantity. Most of the corresponding alkylamino-compounds were not similarly obtainable from N-*methyl*- or NN-*diethyl-serine* (*α-methylamino*- or *α-diethylamino-β-hydroxypropionic acid*).

THE amino-derivatives of acrylic acid are comparatively difficult of access, one of the easier routes being the condensation of acetamide with pyruvic acid, followed by the elimination of one molecule of acetamide from the diacetamidopropionic acid (I) so obtained (Bergmann and Grafe, *Z. physiol. Chem.*, 1930, **187**, 187):

$$\underset{\text{(I.)}}{CMe(NHAc)_2\cdot CO_2H} \longrightarrow \underset{\text{(II.)}}{CH_2{:}C(NHAc)\cdot CO_2H} + NH_2Ac$$

This method is of limited application; the synthesis of derivatives of α-acetamidoacrylic acid (II) in this way is at the best troublesome and is usually impossible owing to the reactivity of the acid towards the usual reagents. Diacetamidopropionic acid (I) is more stable but only the acid itself decomposes to the unsaturated compound.

Methyl α-acetamidoacrylate has been obtained from the acid by means of the silver salt and methyl iodide, but even here direct esterification was not successful and the use of methyl sulphate was also unsatisfactory. Since methyl α-acetamidoacrylate afforded a polymer with somewhat unusual properties, syntheses in this series were further investigated. In the case of α-acetamidocinnamic acid the *amide* could be prepared quite easily from the corresponding azlactone and ammonia:

$$\begin{array}{l} CHPh{:}C\cdot CO \\ \qquad\quad \diagdown\!\!>O \\ \qquad\quad N{:}CMe \end{array} + NH_3 \longrightarrow CHPh{:}C(NHAc)\cdot CO\cdot NH_2$$

but even in this case the *methyl* ester was best obtained from the silver salt; dehydration of the amide to the nitrile could not be accomplished owing to complete decomposition. The azlactone of α-acetamidoacrylic acid is unknown and in consequence other possible methods for the synthesis of the amide and of other derivatives had to be devised.

The starting material was serine (*Org. Synth.*, 1940, **20**, 81) which was esterified and converted into methyl β-chloro-α-aminopropionate hydrochloride, $CH_2Cl\cdot CH(NH_2,HCl)\cdot CO_2Me$ (III), by a slight modification of the method of Fischer and Rasche (*Ber.*, 1907, **40**, 3723). Not very large amounts of this substance could be obtained because the yields are extremely irregular and appear to depend on the purity of both the ester hydrochloride and the phosphorus pentachloride. *Methyl β-chloro-α-acetamidopropionate* (IV) was produced when (III) was boiled with acetyl chloride in benzene suspension, and (IV) was converted by alkali into *α-acetamidoacrylamide* (V), methyl α-acetamidoacrylate, or methyl α-acetamido-β-methoxypropionate (VI) according to the conditions:

$$\underset{\text{(IV.)}}{CH_2Cl\cdot CH(NHAc)\cdot CO_2Me} \longrightarrow \begin{cases} CH_2{:}C(NHAc)\cdot CO\cdot NH_2 & \text{(V.)} \\ CH_2{:}C(NHAc)\cdot CO_2Me & \\ MeO\cdot CH_2\cdot CH(NHAc)\cdot CO_2Me & \text{(VI.)} \end{cases}$$

The methoxy-ester (VI), previously synthesised by Synge (*Biochem. J.*, 1939, **33**, 1931) using a different method, was formed when methyl-alcoholic potash was used. Removal of hydrogen halide with ethereal ammonia furnished mainly the methyl acrylate accompanied by a small quantity of the amide (V). The latter, however, must have been derived directly from (IV) because methyl acetamidoacrylate is either unreactive or suffers complete decomposition when mixed with ammonia in various proportions. In fact, (IV) with cold concentrated aqueous ammonia yielded β-*chloro-α-acetamidopropionamide*, $CH_2Cl{\cdot}CH(NHAc){\cdot}CO{\cdot}NH_2$ (VII), but useful quantities were unobtainable by this method.

Attempts to prepare the amide (VII) in larger amounts were unsuccessful. Neither α-*amino-β-hydroxypropionamide hydrochloride*, $HO{\cdot}CH_2{\cdot}CH(NH_2,HCl){\cdot}CO{\cdot}NH_2$, nor its N-*acetyl* derivative (IX), prepared by the hydrolysis of *methyl α-acetamido-β-acetoxypropionate* (VIII) with ammonia, would react with a halogenating agent to yield the corresponding β-chloro-compound, *e.g.*, (VII) :

$$HO{\cdot}CH_2{\cdot}CH(NH_2,HCl){\cdot}CO_2Me \xrightarrow{AcCl} \underset{(VIII.)}{AcO{\cdot}CH_2{\cdot}CH(NHAc){\cdot}CO_2Me} \xrightarrow{aq.\ NH_3} \underset{(IX.)}{HO{\cdot}CH_2{\cdot}CH(NHAc){\cdot}CO{\cdot}NH_2} \xrightarrow{PCl_5} (VII)$$

nor was it possible to dehydrate (IX) to the acryloamide (V). A similar difficulty attended the replacement of the hydroxyl group in *methyl α-diethylamino-β-hydroxypropionate* (XI), prepared from methyl α-bromo-β-methoxypropionate (X) :

$$\underset{(X.)}{MeO{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2Me} \longrightarrow MeO{\cdot}CH_2{\cdot}CH(NEt_2){\cdot}CO_2Me \longrightarrow \underset{(XI.)}{HO{\cdot}CH_2{\cdot}CH(NEt_2){\cdot}CO_2H}$$

Reaction between (XI) and phosphorus pentachloride afforded a base containing less than 25% of the calculated percentage of chlorine. Since alkali failed to remove all the halogen the experiments in this case were not pursued further.

The *N*-methyl derivatives of α-aminoacrylic acid could not be prepared. Direct methylation of α-acetamidoacrylic acid or of αα-diacetamidopropionic acid and condensation of pyruvic acid with acetomethylamide failed. Next, the reactions of the *N*-methyl derivatives of serine were examined. Ethyl α-bromo-β-ethoxypropionate (XII) (Wood and Vigneaud, *J. Biol. Chem.*, 1940, **134**, 414) gave α-*methylamino-β-ethoxypropionomethylamide* (XIII) and thence α-*methylamino-β-hydroxypropionic acid* (XIV) :

$$\underset{(XII.)}{EtO{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2Et} \longrightarrow \underset{(XIII.)}{EtO{\cdot}CH_2{\cdot}CH(NHMe){\cdot}CO{\cdot}NH_2} \longrightarrow \underset{(XIV.)}{HO{\cdot}CH_2{\cdot}CH(NHMe){\cdot}CO_2H}$$

No difficulty was encountered in obtaining *methyl α-acetomethylamido-β-acetoxypropionate* $AcO{\cdot}CH_2{\cdot}CH(NMeAc){\cdot}CO_2Me$, from the *hydrochloride* of the *methyl* ester of (XIV), but, unlike the unmethylated homologue, it could not be satisfactorily hydrolysed to the β-hydroxy-compound.

On the other hand, although *methyl β-chloro-α-methylaminopropionate hydrochloride* (XV) was produced by addition of phosphorus pentachloride to a chloroform solution of the methyl ester hydrochloride, the halogen atom was replaced by an acetoxy-group when (XV) was warmed with acetyl chloride, yielding the *methyl α-methylamino-β-acetoxypropionate hydrochloride* (XVI), and not the *N*-acetyl derivative :

$$\underset{(XV.)}{CH_2Cl{\cdot}CH(NHMe,HCl){\cdot}CO_2Me} \longrightarrow \underset{(XVI.)}{AcO{\cdot}CH_2{\cdot}CH(NHMe,HCl){\cdot}CO_2Me}$$

The ester (XVI) is apparently also formed when methyl α-acetomethylamido-β-hydroxypropionate is boiled first with acetyl chloride and then with phosphorus pentachloride, but the melting point is somewhat lower and there is a slight depression when the substance is mixed with (XVI). The only alternative structure for (XVI) is methyl β-chloro-α-methylaminopropionate acetate, $CH_2Cl{\cdot}CH(CO_2Me){\cdot}NHMe,AcOH$, but the substance contained *ionic* halogen and did not afford an unsaturated derivative when warmed with piperidine.

Experimental.

Acetamidoacrylic Acid.—αα-Diacetamidopropionic acid was prepared from acetamide (480 g.) and freshly distilled pyruvic acid (390 g.) (Bergmann and Grafe, *loc. cit.*). The yield after three extractions with ethyl acetate was 357 g. (43%), the acid separating from water or ethanol in needles, m. p. 195—196° (decomp.) [Bergman and Grafe record m. p. 189—190° (corr.; decomp.)]. The extracts afforded a mixture (132 g.) of this acid with α-acetamidoacrylic acid. The total quantity of the acetamidoacrylic acid finally obtained from the above products was 136 g. (40%); this acid crystallised from ethanol in

needles, m. p. 204° (decomp.) [Bergmann and Grafe give m. p. 198—200° (corr.)]. For complete conversion of the diacetamido-compound into the unsaturated acid, the former must be mixed with *cold* glacial acetic acid, the temperature then being gradually raised to the boiling point.

Acetamidoacrylic acid decomposes when mixed with thionyl chloride (alone or in pyridine), phosphorus pentachloride, or phosphorus oxychloride. Direct esterification failed. The silver salt (80%) was precipitated by the addition of a slight excess of concentrated silver nitrate solution to a solution of the sodium salt of the acid; unchanged acid could be recovered by acidifying the filtrate with a slight excess of concentrated hydrochloric acid. *Methyl α-acetamidoacrylate*, obtained by boiling the silver salt with excess of methyl iodide and a small quantity of quinol, separated from light petroleum (b. p. 40—60°) in short prisms, m. p. 52—54° (yield 66—70% based on the silver salt) and distils without decomposition (b. p. 104°/8 mm.) but is liable to polymerise unless quinol is present (Found: C, 50·5; H, 6·2; *M*, 154. $C_6H_9O_2N$ requires C, 50·3; H, 6·3%; *M*, 143). The ester when first prepared has a pleasant heliotrope odour, but when kept develops the odour characteristic of pyruvic acid. It is unsaturated to permanaganate and quickly decolorises bromine water. The preparation using methyl sulphate is illustrated in the two typical examples below:

(i) A solution of the acid (6 g.) in warm methanol (100 c.c.) was made slightly alkaline to methyl-orange with 6% sodium methoxide solution, and to it were added quinol (1 g.), anhydrous sodium carbonate (3·0 g.), and methyl sulphate (9·0 g.). The liquid was boiled under reflux for 2 hours and then cooled, an excess of dry ether was added, and the precipitated sodium salts were filtered off. The filtrate was distilled to dryness in a vacuum, and the residue repeatedly extracted with ether. The yield of recrystallised ester was 3 g. (45%).

(ii) A methanolic (50 c.c.) solution of the acid (5 g.), when boiled under reflux for 20 hours with quinol (1 g.), sodium carbonate (6 g.), and methyl sulphate (9 c.c.) and then treated as in (i), gave 2·0 g. (36%) of recrystallised ester.

Synthesis of Methyl β-Chloro-α-acetamidopropionate from Serine.—Methyl β-chloro-α-aminopropionate hydrochloride (III) was prepared by Fischer and Rasche's method (*loc. cit.*), adapted for larger quantities. A cooled suspension of dry serine methyl ester hydrochloride (Fischer and Suzuki, *Ber.*, 1907, **40**, 4193) (22·3 g.) in acetyl chloride (200 c.c.) was stirred vigorously during the addition of phosphorus pentachloride (34 g.). There was a slow evolution of hydrogen chloride and at the end of two hours the liquid which had become homogeneous deposited the chloro-ester hydrochloride as a white powder. This was filtered off and washed with acetyl chloride and petrol; yield, 12·6 g. (50·5%). A further quantity (6·6 g.) of very impure material could be obtained from the filtrate by precipitation with light petroleum, but was not easily purified and was unsuitable for further synthetic work.

The chloro-ester hydrochloride (56 g.) was suspended in dry benzene (400 c.c.) and boiled under reflux with freshly distilled acetyl chloride (45 c.c.) until dissolution was complete. Addition of an excess of light petroleum (b. p. 40—60°) precipitated *methyl β-chloro-α-acetamidopropionate* (IV) which crystallised from ether–light petroleum (b. p. 40—60°) in micro-crystals, m. p. 79—80° (24·5 g., 46%) (Found: C, 40·5; H, 5·7; Cl, 19·5. $C_6H_{10}O_3NCl$ requires C, 40·1; H, 5·6; Cl, 19·8%).

Removal of Hydrogen Chloride from Methyl β-Chloro-α-acetamidopropionate.—(a) *With potassium methoxide.* The chloro-ester (6·5 g.) was set aside with 2N-potassium methoxide (18 c.c.) and quinol (0·05 g.) for several hours, filtered, and evaporated to dryness in a vacuum. A warm ethereal extract deposited, on cooling, a crystalline product, m. p. 65—70°. After three extractions with boiling light petroleum (b. p. 40—60°), it crystallised from ether in stellate clusters, m. p. 72—73° (2·4 g., 38%). The substance was evidently methyl α-acetamido-β-methoxypropionate (Synge, *loc. cit.*, gave m. p. 70—71°) but could not be entirely freed from the accompanying methyl acetamidoacrylate which could be detected by its odour (Found: C, 48·7; H, 7·2; N, 7·8. Calc. for $C_7H_{13}O_4N$: C, 48·0; H, 7·4; N, 8·0%). The light petroleum extracts afforded the acrylate in 37% yield.

(b) *With methyl-alcoholic potash.* The ester (1·8 g.) was mixed with a solution of potassium hydroxide (0·6 g.) and quinol (0·01 g.) in methanol (5 c.c.). Potassium chloride was precipitated, heat being evolved, and the odour of methyl acetamidoacrylate became perceptible. Filtration and removal of the solvent left a residue from which 0·4 g. (28%) of the ester was obtained.

(c) *With methyl-alcoholic ammonia.* The chloro-ester (0·45 g.) with 25% methanolic ammonia (5 c.c.) (but no quinol) furnished polymerised methyl acetamidoacrylate.

(d) *With ethereal ammonia.* The chloro-ester (3 g.) was boiled with dry ether (300 c.c.), filtered from a small amount of undissolved substance, and, following the addition of a small quantity of quinol, saturated with ammonia. After being kept in a refrigerator for 2 days, the liquid was filtered and the solvent removed in the usual manner. The semi-solid residue was extracted with two successive quantities of boiling light petroleum (b. p. 40—60°) which, when evaporated, yielded methyl acetamidoacrylate (1·3 g., 54%). The residue from the extractions was recrystallised from ethanol, whence separated *α-acetamidoacrylamide* (V) as clusters of prisms, m. p. 161—162° (Found: C, 47·2; H, 6·3; N, 21·7. $C_5H_8O_2N_2$ requires C, 46·9; H, 6·2; N, 21·9%). The substance rapidly decolorised bromine water and alkaline permanganate solution.

(e) *With ethereal piperidine.* A filtered solution of the ester (1·8 g.) in ether (150 c.c.) containing quinol was mixed with piperidine (0·85 g.). The theoretical amount of piperidine hydrochloride was precipitated and filtered off. Distillation of the solvent gave nearly pure methyl α-acetamidoacrylate (0·8 g., 56%).

Derivatives of Serine.—*β-Chloro-α-acetamidopropionamide* (VII) was formed by the gradual addition of methyl β-chloro-α-acetamidopropionate (3·0 g.) to ammonia (*d*, 0·88; 20 c.c.), containing a little quinol and cooled in a freezing mixture. The mixture was shaken from time to time and after about 1½ hours the dark-red, nearly homogeneous solution deposited a small quantity of the amide which separated from ethanol in micro-crystals, m. p. 167° (decomp.) (Found: C, 36·8; H, 5·6; N, 16·7; Cl, 21·9. $C_5H_9O_2N_2Cl$ requires C, 36·5; H, 5·5; N, 17·0; Cl, 21·6%).

The preparation of *methyl α-acetamido-β-acetoxypropionate* (VIII) was carried out by boiling under reflux a suspension of serine methyl ester hydrochloride (17·5 g.) in benzene (100 c.c.) with acetyl chloride (18 c.c.) for 2 hours, the reaction being completed by the further addition of acetyl chloride (5 c.c.).

Removal of the solvent from the now homogeneous solution yielded the diacetyl compound, b. p. 160°/8 mm., 135°/0·8 mm. (22 g., 96·5%). The substance solidified below 0° but could not be recrystallised satisfactorily (Found : C, 47·9; H, 6·5; N, 7·5. $C_8H_{13}O_5N$ requires C, 47·3; H, 6·4; N, 6·9%). Conversion into α-acetamido-β-hydroxypropionamide (IX) took place when a solution of (VIII) (22 g.) in methanol (100 c.c.) was saturated with ammonia at 0° and set aside for 2 days. Evaporation of the solvent yielded the amide which, after rubbing with methanol, crystallised from ethanol; m. p. 138—139°; yield, 7·5 g. (47·5%) (Found : C, 41·2; H, 6·6; N, 19·1. $C_3H_{10}O_2N_2$ requires C, 41·1; H, 6·9; N, 19·2%). A further small quantity of the substance could be obtained by saturating the methanolic extract with ammonia. The amide could also be prepared by evaporating, on the steam-bath, an aqueous-ammoniacal solution of the diacetyl compound, but the subsequent purification was more laborious.

Substitution of the hydroxyl group by halogen was impossible owing to the decomposition caused by the usual reagents. Direct dehydration by heat was also impossible, only very slight reaction occurring at 160—180°.

α-Amino-β-hydroxypropionamide hydrochloride resulted when the methyl ester hydrochloride was mixed with methanolic ammonia below 0°. The residue obtained by distilling off the solvent in a vacuum was dissolved in methanol, filtered, and again evaporated. The residue separated from a concentrated solution in the same solvent as a crystalline power, m. p. 192—193° (decomp.) (Found : C, 25·6; H, 7·1. $C_3H_9O_2N_2Cl$ requires C, 25·6; H, 6·4%).

Derivatives of Diethylaminopropionic Acid.—Methyl α-bromo-β-methoxypropionate (30 g.) was boiled for 2 hours under reflux with diethylamine (30 g.) and methanol (30 c.c.), excess of alkali added, and the base extracted with ether. The ethereal layer yielded a product containing unchanged bromo-ester. The mixture was shaken with dilute acetic acid and extracted with ether, and the aqueous layer basified and extracted as before, thus yielding pure *methyl α-diethylamino-β-methoxypropionate*, b. p. 83—85°/8 mm., (12·3 g., 43%) (Found : 57·5; H, 9·8. $C_9H_{19}O_3N$ requires C, 57·1; H, 10·1%).

Methyl α-diethylamino-β-hydroxypropionate, b. p. 100°/10 mm., was prepared by boiling the methoxy-ester (16 g.) with hydrobromic acid (48%; 200 c.c.) for 2 hours. After removal of the acid, etc., in a vacuum, water (250 c.c.) was added, the solution distilled to dryness, and the procedure repeated using the same quantity of methanol. Finally, a methanolic solution of the residue was saturated with dry hydrogen chloride and then evaporated to dryness, and the residue basified. The ethereal extract of the liquid was dried (Na_2SO_4) and from it were isolated 2 g. (13·5%) of the amino-ester (Found : C, 55·1; H, 9·6; N, 8·2. $C_8H_{17}O_3N$ requires C, 54·9; H, 9·7; N, 8·0%).

Attempted Preparation of Methyl β-Chloro-α-diethylaminopropionate.—The hydrochloride of the above ester (22 g.), dried over phosphoric oxide, was dissolved in freshly redistilled acetyl chloride (200 c.c.) and stirred with phosphorus pentachloride (26 g., 25% excess) for 2 hours, after which the liquid was boiled under reflux until no more hydrogen chloride was evolved (20 minutes). The base obtained by this reaction had b. p. 89°/8 mm. and contained only a small proportion of the theoretical quantity of chlorine (see analysis), but even this small amount was not removed by ethereal piperidine or methanolic ammonia over a period of a week and no further attempt was made to obtain the pure chloro-ester (Found : C, 52·8; H, 9·1; Cl, 4·4. Calc. for $C_9H_{16}O_3NCl$: C, 49·6; H, 8·3; Cl, 4·4%). It is evident that not more than about 25% of the mixture was the required base.

Acetamidocinnamic Acid Derivatives.—The azlactone of α-acetamidocinnamic acid (*Org. Synth.*, Coll. Vol. II, 1) (90 g.) was suspended in ethanol (500 c.c.) and saturated with ammonia at 0°. The precipitate was washed with the solvent and crystallised therefrom. *α-Acetamidocinnamide* separated in colourless needles, m. p. 205° (decomp.) (68 g., 70%) (Found : C, 64·3; H, 5·7. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9%).

The *methyl* ester, prepared by boiling the silver salt of the acid with methyl iodide, crystallised from benzene in fine needles, m. p. 119—120° (Found : C, 65·8; H, 6·2; N, 6·2. $C_{12}H_{13}O_2N$ requires C, 65·8; H, 5·9; N, 6·4%).

Methylamino-derivatives.—(a) *Attempted preparation of α-acetomethylamidoacrylic acid.* When freshly distilled pyruvic acid (1 mol.) was mixed with acetomethylamide (2 mols.), heat was evolved but no condensation took place, in contrast to the corresponding experiments with acetamide. The experiment, repeated with use of diethylamine, piperidine, or sodium ethoxide as catalyst, was equally unfruitful, nor was it possible to methylate α-acetamidoacrylic acid directly with either methyl sulphate or methyl *o*-nitrobenzenesulphonate.

(b) *Derivatives of α-methylamino-β-hydroxypropionic acid.* Ethyl α-bromo-β-ethoxypropionate (Wood and Vigneaud, *loc. cit.*) (40 g.) was heated for 12 hours at 100° with 33% ethanolic methylamine (50 g.) in a sealed tube. Addition of dry ether precipitated most of the excess of methylamine as hydrobromide. This was filtered off, the filtrate extracted with dilute acid, and the aqueous layer concentrated. An excess of solid potassium carbonate was then added, the liberated base extracted with ether, and the solution dried (K_2CO_3). Removal of the ether yielded *α-methylamino-β-ethoxypropionomethylamide* (XIII), b. p. 86°/1 mm. (14·7 g., 52%) (Found : C, 52·2; H, 10·1; N, 18·2. $C_7H_{16}O_2N_2$ requires C, 52·5; H, 10·0; N, 17·5%). Hydrolysis was carried out by boiling the amide with excess of 48% hydrobromic acid, the hydrobromide being isolated in the usual way; the free acid was obtained by boiling an aqueous solution of this salt with freshly precipitated white lead oxide as described in the next experiment.

It was found advantageous (cf. preparation of serine, *Org. Synth.*, *loc. cit.*) to use the α-bromo-β-ethoxy-acid for the condensation with methylamine. The ester was hydrolysed with cold sodium hydroxide, and a nearly theoretical yield of the acid obtained by acidification with 7N-sulphuric acid and extraction with ether. The product (352 g.) was heated with 30% aqueous methylamine (700 g.) at 100° in an autoclave for 20 hours. After hydrolysis with hydrobromic acid, the methylamino-acid was boiled with lead oxide until no further bromine ions were present in the solution. Several successive quantities of the oxide were necessary, the lead bromide being filtered off before each new addition. The final filtrate was heated to the boiling point and saturated with hydrogen sulphide. Removal of the precipitated lead sulphide was followed by evaporation in a vacuum. The residue, washed with ethanol, was recrystallised from this solvent with the addition of a very small amount of water, and the *α-methylamino-β-hydroxy-*

propionic acid (XIV) dried in a vacuum over phosphoric oxide; m. p. 210° (decomp.); yield, 66 g. (31% based on the bromo-acid) (Found: C, 40·4; H, 7·4; N, 11·8. $C_4H_9O_3N$ requires C, 40·3; H, 7·6; N, 11·8%).

Methyl α-methylamino-β-hydroxypropionate hydrochloride was prepared by saturating a solution of the acid (10 g.) in methanol (250 c.c.) with dry hydrogen chloride. After isolation by the usual method it was dried over phosphoric oxide (yield, 12·4 g., 86·5%). Recrystallisation from ethanol–light petroleum (b. p. 60—80°) afforded a product, m. p. 115—116° (Found: C, 35·4; H, 6·9; N, 8·7; Cl, 21·2. $C_5H_{12}O_3NCl$ requires C, 35·4; H, 7·1; N, 8·3; Cl, 20·9%).

Methyl α-acetomethylamido-β-acetoxypropionate (4·7 g., 65%) resulted when a mixture of the above methyl ester (5·65 g.), acetyl chloride (7 g.), and benzene (50 c.c.) was boiled under reflux for 24 hours. It had b. p. 132°/0·3 mm. (Found: C, 49·9; H, 6·9. $C_9H_{15}O_5N$ requires C, 49·8; H, 6·9%). Unlike that of the unmethylated derivative, its satisfactory hydrolysis could not be achieved. Decomposition ensued when ammonia was added.

Methyl β-Chloro-α-methylaminopropionate Hydrochloride (XV).—Methyl α-methylamino-β-hydroxypropionate (2 g.) was dissolved in chloroform (10 c.c.), and phosphorus pentachloride (2·7 g.) added in three portions to the liquid cooled in water. The mixture was then cooled to below 0°. After 2 days, the *chloro*-ester *hydrochloride* was deposited as a white solid (1·1 g.). This was washed with chloroform and ether and recrystallised from methanol–ether whence it separated in stellate clusters, m. p. 143° (decomp.) (Found: C, 31·9; H, 5·9; N, 7·2; Cl, 37·2. $C_5H_{11}O_2NCl_2$ requires C, 31·9; H, 5·9; N, 7·4; Cl, 37·8%). The same substance was obtained by mixing, with ice-cooling, the β-hydroxy-derivative (2 g.), freshly distilled acetyl chloride (10 c.c.) and phosphorus pentachloride (2·7 g.); the reaction was completed by boiling the liquid for 30 minutes. When cold, a small crystalline deposit (0·7 g.) was formed. The melting point, after crystallisation from ethanol, was slightly lower than that given above (Found: C, 31·8; H, 6·2%).

Reaction of (XV) *with Acetyl Chloride.*—The dichloro-compound (0·4 g.) in benzene (20 c.c.) was boiled under reflux with acetyl chloride (0·3 c.c.) until dissolution was almost complete. After decantation and evaporation to dryness, the residual syrup was carefully washed with ether containing a trace of ethanol and recrystallised first from this mixture and then from ether–methanol. The m. p. was then 118—119° and was slightly depressed when the substance was mixed with that described in the next paragraph. The analytical figures appeared to indicate the identity of the two compounds (Found: C, 40·4; H, 6·8; N, 6·9; Cl, 17·4. Calc. for $CH_2Cl{\cdot}CH(NMeAc){\cdot}CO_2Me$: C, 43·4; H, 6·2; N, 7·3; Cl, 18·4%). Other experiments using different samples of the starting material yielded compounds with slightly lower melting points, the analytical figures being nearer those below. It is possible that these were mixtures.

Methyl α-methylamino-β-acetoxypropionate hydrochloride (XVI) was formed in an experiment designed to prepare in one operation the β-chloro-*N*-acetyl ester from methyl α-methylamino-β-hydroxypropionate hydrochloride. The latter (7 g.) was boiled under reflux with acetyl chloride (15 c.c.) for 1 hour and then treated with phosphorus pentachloride (7·7 g.). The liquid was boiled for a further 15 minutes and set aside at 0° overnight. The supernatant liquid was decanted and the residue washed with ether, mixed with alcohol and ether to decompose any remaining phosphorus halides, and after filtration again washed with ether. Three recrystallisations from ethanol furnished the acetoxy-ester, m. p. 110—112° (Found: C, 39·5; H, 6·7; N, 6·7; Cl, 16·6. $C_7H_{14}O_4NCl$ requires C, 39·7; H, 6·6; N, 6·6; Cl, 16·8%).

Attempted Replacement of the Hydroxyl Group by Bromine.—Methylaminohydroxypropionic acid (1 g.) was mixed with 80% hydrobromic acid (4 g.). After 48 hours, the liquid was distilled in a vacuum to dryness and the residue allowed to crystallise in a vacuum desiccator over phosphoric oxide. The crystals were mixed with absolute ethanol and the process repeated. The *hydrobromide* so obtained had a somewhat indefinite m. p. of 160° (decomp.) and may have contained traces of the β-bromo-derivative (Found: C, 23·5; H, 5·0; N, 6·7; Br, 40·8. $C_4H_{10}O_2NBr$ requires C, 24·0; H, 5·0; N, 7·0; Br, 40·0%).

The foregoing has been put on record as the investigation has now been discontinued. The author thanks Messrs. Imperial Chemical Industries Limited, Dyestuffs Division, for a grant and for gifts of chemicals.

THE UNIVERSITY, LEEDS. [*Received, March 8th,* 1949.]

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420. *Aryl-2-halogenoalkylamines. Part II.*

By J. L. EVERETT and W. C. J. ROSS.

Ross (this vol., p. 183) described the preparation and some reactions of a series of aryl-2-halogenoethylamines. In view of the interesting biological activity of these compounds this work has now been extended. A further series of arylhalogenoethylamines and a number of arylhalogenopropylamines have been examined. The effect of structural modification on the reactivity of the halogen atoms (as measured by the rate of hydrolysis in aqueous acetone) is discussed.

MANY aryldi-(2-halogenoethyl)amines, a number of which has recently been described (Ross, this vol., p. 183), show interesting biological properties, notably an inhibiting effect on the growth of certain transplantable rat tumours (*e.g.*, the Walker carcinoma: Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824; British Empire Cancer Campaign Report for 1947). This work has now been extended.

The results so far obtained suggest that, in order to exhibit cytotoxic activity, the compound

must possess two reactive 2-halogenoalkyl groups attached to a nitrogen atom (though these need not necessarily be attached to the same nitrogen atom—see below), and that substitution in the aromatic nucleus tending to reduce the chemical reactivity of the halogen atoms (as measured by the rate of hydrolysis in aqueous acetone) also reduces the biological activity. Compounds with only one halogenoethylamino-group are inactive.

Most of the new *NN*-di-(2-halogenoethyl) compounds now described have been made by the general methods detailed in Part I; these derivatives are listed, together with related compounds, in Table I. For the preparation of aryl-di-(2-hydroxyethyl)amines the action of ethylene oxide on the amine is preferred since this leads to purer products: it has been found desirable to carry out the reaction at 150° with all amines as monosubstitution may occur at lower temperatures, particularly with the less basic amines.

The action of ethylene oxide on ethyl *p*-aminobenzoate yields the NN-*di*-(2-*hydroxyethyl*) derivative which has been converted into the corresponding *dichloro*-compound. This ester may be hydrolysed by use of concentrated hydrochloric acid to give the acid which was previously obtained by the oxidation of the aldehyde (Part I); esterification with diazomethane affords the *methyl* ester.

Benzenediazonium chloride couples with *NN*-di-(2-hydroxyethyl)aniline to form NN-*di*-(2-*hydroxyethyl*)-p-*aminoazobenzene* which may be converted into the *dichloro*-compound. This derivative may also be obtained by the direct coupling of benzenediazonium chloride with *NN*-di-(2-chloroethyl)aniline; p′-*nitro*-NN-*di*-(2-*chloroethyl*)-p-*aminoazobenzene* is similarly obtained from the amine and *p*-nitrobenzenediazonium chloride. These two azo-compounds were prepared with the intention of obtaining active coloured derivatives the location of which in the treated animal's tissue could be determined. The more intensely coloured *p*-nitro-compound was inactive but the other was effective, and it was considered possible that reduction of the azo-link might occur *in vivo*. It was therefore of interest to prepare and examine *NN*-di-(2-chloroethyl)-*p*-phenylenediamine.

Attempts to obtain this amine by the reduction of the azo-compound were unsuccessful owing to the difficulty of separating the two products which are formed. The desired *p*-amino-derivative was eventually obtained by the reduction of p-*nitroso*-NN-(2-*dichloroethyl*)*aniline* which could be prepared by direct nitrosation of the aniline in acid solution. *NN*-Di-(2-chloro-ethyl)-*p*-phenylenediamine was isolated as its *monohydrochloride*; this is a water-soluble substance of high toxicity and powerful vesicant action. *Acetyl* and *benzoyl* derivatives were prepared by the action of acetic anhydride and benzoyl chloride respectively on ice-cold aqueous suspensions of the free base.

It is known that, in the non-aromatic series of chloroethylamines, the two halogenoethylamino-groups essential for activity need not be situated on the same nitrogen atom, for example, *NN′*-di-(2-chloroethyl)piperazine is an effective compound. It was hoped to prepare derivatives of the phenylenediamines in which each nitrogen atom carried one chloroethyl group but this has not been possible on account of the unstable nature of the intermediate hydroxyethyl compounds which rapidly darken when exposed to air and which did not give homogeneous products when chlorinated. A compound of the desired structure was, however, obtained in the following way: *oo′*-dinitrodiphenyl was reduced with stannous chloride to give the diamine (an attempted reduction using a Raney nickel catalyst gave only benzcinnoline) which was converted successfully into the *bistoluene*-p-*sulphonamide*, the *dimethylbistoluene*-p-*sulphonamide*, and NN′-*dimethyl*-oo′-*diaminodiphenyl*. Chlorination of the NN′-*di*-(2-*hydroxyethyl*) derivative obtained by the action of ethylene oxide on this diamine afforded NN′-*dimethyl*-NN′-*di*-(2-*chloroethyl*)-oo′-*diaminodiphenyl*. This compound is not an effective tumour-growth inhibitor but it was later found that diphenyl derivatives as a class are not active, possibly on account of their very low water solubility, for example, NNN′N′-*tetra*-(2-*chloroethyl*)-oo′-*diaminodiphenyl* and -*pp′*-diaminodiphenyl (Part I) are also inactive.

It had previously been found that 2-aminofluorene reacts at 90° to give a monosubstituted product but when the reaction is carried out at a higher temperature NN-*di*-(2-*hydroxyethyl*)-2-*aminofluorene* is formed; this may be converted into the *dichloro*-derivative in the usual way.

The derivatives listed in Table I represent variations of the halogen in the side chain and also of the nature of the aromatic nucleus carrying this side chain. Attention has also been paid to varying the nature of the halogenoalkyl group. Table II shows a series of arylhalogenopropyl-amines and related compounds. 2-Halogeno-*n*-propyl derivatives were obtained by chlorinating the products of the reaction of arylamines with propylene oxide. It is known that in its reactions with amines propylene oxide undergoes ring opening almost exclusively in the direction leading to the formation of 2-hydroxy-*n*-propyl derivatives; in the case of disubstituted compounds

TABLE I.

Aryl-2-halogenoethylamines and related compounds.

Compound	M. p.	Crystal form	*S*	Formula	Found, % C	Found, % H	Found, % N	Required, % C	Required, % H	Required, % N
NN-*Di*-(2-*iodoethyl*)*aniline*	—	(Oil)	—	$C_{10}H_{13}NI_2$	(I = 62·8)			(I = 63·3)		
NN-*Di*-(2-*hydroxyethyl*)-p-tert.-*butylaniline* *	114—115°	Plates	C	$C_{14}H_{23}O_2N$	70·7	9·7	—	70·9	9·8	—
NN-*Di*-(2-*chloroethyl*)-p-tert.-*butylaniline* *	—	(Oil)	—	$C_{14}H_{21}NCl_2$	61·6	7·9	—	61·3	7·7	—
NN-*Di*-(2-*hydroxyethyl*)-vic.-m-*xylidine*	—	(Oil)	—	$C_{12}H_{19}O_2N$	68·9	9·2	—	69·0	9·2	—
NN-*Di*-(2-*chloroethyl*)-vic.-m-*xylidine*	32	Plates	D	$C_{12}H_{17}NCl_2$	58·8	6·9	—	58·5	7·0	—
p-*Nitroso*-NN-*di*-(2-*chloroethyl*)*aniline*	79—80	Deep green plates	F	$C_{10}H_{12}ON_2Cl_2$	48·8	5·1	11·6	48·6	4·9	11·3
NN-*Di*-(2-*chloroethyl*)-p-*phenylenediamine hydrochloride*	250—260 (decomp.)	Plates	A–F	$C_{10}H_{15}N_2Cl_3$	44·7	5·8	—	44·5	5·6	—
N′-*Acetyl*-NN-*di*-(2-*chloroethyl*)-p-*phenylenediamine*	124—126	Flattened needles	C–D	$C_{12}H_{16}ON_2Cl_2$	52·7	6·0	—	52·4	5·9	—
N′-*Benzoyl*-NN-*di*-(2-*chloroethyl*)-p-*phenylenediamine*	164—165	Fine needles	C	$C_{17}H_{18}ON_2Cl_2$	60·2	5·6	—	60·5	5·4	—
Methyl NN-*di*-(2-*chloroethyl*)-p-*aminobenzoate*	58	Plates	E	$C_{12}H_{15}O_2NCl_2$	52·2	5·7	—	52·2	5·5	—
Ethyl NN-*di*-(2-*hydroxyethyl*)-p-*aminobenzoate*	70	Small prisms	C	$C_{13}H_{19}O_4N$	61·7	7·2	—	61·6	7·6	—
Ethyl NN-*di*-(2-*chloroethyl*)-p-*aminobenzoate*	62	Flattened needles	G	$C_{13}H_{17}O_2NCl_2$	53·8	5·9	—	53·8	5·9	—
o-*Xenyldi*-(2-*hydroxyethyl*)*amine*	—	(Oil)	—	$C_{16}H_{19}O_2N$	74·7	7·5	—	74·7	7·4	—
o-*Xenyldi*-(2-*chloroethyl*)*amine*	61	Needles	D	$C_{16}H_{17}NCl_2$	65·0	5·9	4·7	65·3	5·8	4·8
o-*Xenyldi*-(2-*bromoethyl*)*amine*	81	Needles	E	$C_{16}H_{17}NBr_2$	50·5	4·7	—	50·2	4·5	—
o-*Xenyldi*-(2-*iodoethyl*)*amine*	112	Needles	H	$C_{16}H_{17}NI_2$	40·5	3·5	—	40·3	3·6	—
p-*Xenyldi*-(2-*bromoethyl*)*amine*	103	Plates	H	$C_{16}H_{17}NBr_2$	50·7	4·5	—	50·2	4·5	—
p-*Xenyldi*-(2-*iodoethyl*)*amine*	124	Plates	E	$C_{16}H_{17}NI_2$	41·0	3·7	—	40·3	3·6	—
NN′-*Dimethyl*-NN′-*di*-(2-*hydroxyethyl*)-oo′-*diaminodiphenyl*	75—76	Prisms	E	$C_{18}H_{24}O_2N_2$	71·6	8·1	—	71·9	8·1	—
NN′-*Dimethyl*-NN′-*di*-(2-*chloroethyl*)-oo′-*diaminodiphenyl*	41—43	Prisms	D	$C_{18}H_{22}N_2Cl_2$	64·3	6·4	—	64·1	6·6	—
NNN′N′-*Tetra*-(2-*chloroethyl*)-oo′-*diaminodiphenyl*	76—78	Prisms	A	$C_{20}H_{24}N_2Cl_4$	55·5	5·6	—	55·3	5·6	—
NN-*Di*-(2-*hydroxyethyl*)-p-*aminodiphenyl ether*	98	Plates	C	$C_{16}H_{19}O_2N$	70·0	7·2	—	70·3	7·0	—
NN-*Di*-(2-*chloroethyl*)-p-*aminodiphenyl ether*	—	(Oil)	—	$C_{16}H_{17}ONCl_2$	62·2	5·7	—	61·9	5·5	—
NN-*Di*-(2-*hydroxyethyl*)-p-*aminoazobenzene*	133—135	Deep orange plates	C	$C_{16}H_{19}O_2N_3$	67·9	6·5	—	67·4	6·7	—
NN-*Di*-(2-*chloroethyl*)-p-*aminoazobenzene*	73—75	Pale orange plates	D	$C_{16}H_{17}N_3Cl_2$	59·7	5·4	13·4	59·6	5·3	13·1
p′-*Nitro*-NN-*di*-(2-*chloroethyl*)-p-*aminoazobenzene*	166—167	Deep red plates	I	$C_{16}H_{16}O_2N_4Cl_2$	52·5	4·5	15·2	52·3	4·4	15·3
NN-*Di*-(2-*hydroxyethyl*)-m-*aminostilbene* *	100—101	Cream plates	C	$C_{18}H_{21}O_2N$	76·5	7·4	—	76·3	7·5	—
NN-*Di*-(2-*chloroethyl*)-m-*aminostilbene* *	64—65	Felted needles	D	$C_{18}H_{19}NCl_2$	67·8	5·6	—	67·5	6·0	—
NN-*Di*(-2-*bromoethyl*)-m-*aminostilbene*	67	Plates	D	$C_{18}H_{19}NBr_2$	53·2	4·7	—	52·9	4·7	—
NN-*Di*-(2-*iodoethyl*)-m-*aminostilbene*	95	Needles	E	$C_{18}H_{19}NI_2$	43·3	4·0	—	43·0	3·8	—
NNN′N′-*Tetra*-(2-*hydroxyethyl*)-pp′-*diaminostilbene* *	194—195	Pale yellow plates	B–J	$C_{22}H_{30}O_4N_2$	67·9	8·1	—	68·3	7·8	—
α-*Naphthyldi*-(2-*bromoethyl*)*amine*	43	Thick needles	G	$C_{14}H_{15}NBr_2$	47·4	4·4	—	47·1	4·2	—
α-*Naphthyldi*-(2-*iodoethyl*)*amine*	60	Needles	G	$C_{14}H_{15}NI_2$	37·8	3·6	—	37·3	3·4	—
β-*Naphthyldi*-(2-*bromoethyl*)*amine*	60—62	Plates	D	$C_{14}H_{15}NBr_2$	47·3	4·2	—	47·1	4·2	—
β-*Naphthyldi*-(2-*iodoethyl*)*amine*	73—75	Felted needles	D	$C_{14}H_{15}NI_2$	37·3	3·0	—	37·3	3·4	—
4-*Benzeneazo*-α-*naphthyl*-NN-*di*-(2-*chloroethyl*)*amine*	—	(Oil)	—	$C_{20}H_{19}N_3Cl_2$	64·7	5·5	—	64·5	5·2	—
NN-*Di*-(2-*hydroxyethyl*)-2-*aminofluorene*	137	Small plates	C	$C_{17}H_{19}O_2N$	76·2	7·2	—	75·8	7·1	—
NN-*Di*-(2-*chloroethyl*)-2-*aminofluorene*	138	Plates	C	$C_{17}H_{17}NCl_2$	66·7	5·5	—	66·7	5·6	—

Solvents (*S*) used for crystallisation are: A, methanol; B, ethanol; C, benzene; D, light petroleum (b. p. 40—60°); E, light petroleum (b. p. 60—80°); F, ether; G, pentane; H, *cyclo*hexane; I, acetone; J, water. Since decomposition usually occurs on distillation, no b. p.s are given for the oily materials; the preparations were deemed satisfactory if good analytical figures were obtained for the product.

* These compounds in Tables I and II were prepared by Mr. R. G. W. Spickett who also prepared *NN*-di-(2-chloro-1-*cyclo*hexyl)aniline and assisted in the preparation of the two β-naphthylchloropropylamines by method *b*.

* These compounds in Tables I and II were prepared by Mr. R. G. W. Spickett who also prepared N:N'-di-(2-chloro-1-β-naphthylethyl)amine and assisted in the preparation of the two β-naphthylchloropropylamines by method *b*.

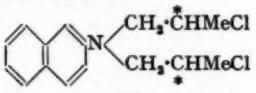
TABLE II.

Arylhalogenopropylamines and related compounds.

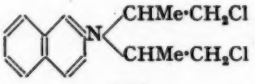
Compound	M. p.	Crystal form	*S*	Formula	Found, % C	Found, % H	Found, % N	Required, % C	Required, % H	Required, % N
N-*Ethyl*-N-(2-*hydroxy*-n-*propyl*)*aniline picrate*	124°	Flattened needles	A	$C_{17}H_{20}O_8N_4$	50·0	5·0	14·4	50·0	4·9	13·7
N-*Ethyl*-N-(2-*chloro*-n-*propyl*)*aniline picrate*	107—108	Needles	A	$C_{17}H_{19}O_7N_4Cl$	48·0	4·7	13·2	47·9	4·5	13·1
NN-*Di*-(2-*chloro*-n-*propyl*)*aniline*	62— 64	Prisms	D	$C_{12}H_{17}NCl_2$	58·8	6·8	—	58·5	7·0	—
p-*Chloro*-NN-*di*-(2-*hydroxy*-n-*propyl*)*aniline*	109—110	Flattened needles	C–E	$C_{12}H_{16}O_2NCl$	59·1	7·5	—	59·2	7·4	—
p-*Chloro*-NN-*di*-(2-*chloro*-n-*propyl*)*aniline*	109—110	Long needles	D	$C_{12}H_{15}NCl_3$	51·8	5·8	5·2	51·4	5·8	5·0
NN-*Di*-(2-*chloro*-n-*propyl*)-p-*anisidine*	68— 70	Thick plates	A	$C_{13}H_{19}ONCl_2$	56·5	7·0	—	56·5	6·9	—
p-*Xenyldi*-(2-*hydroxy*-n-*propyl*)*amine*	117—119	Small prisms	C–E	$C_{18}H_{23}O_2N$	76·0	8·0	—	75·8	8·1	—
p-*Xenyldi*-(2-*chloro*-n-*propyl*)*amine*	94— 97	Prisms	D	$C_{18}H_{21}NCl_2$	67·1	6·6	4·5	67·1	6·6	4·3
p-*Xenyldi*-(2-*bromo*-n-*propyl*)*amine*	84	Needles	D	$C_{18}H_{21}NBr_2$	52·7	5·2	—	52·6	5·2	—
NNN'N'-*Tetra*-(2-*chloro*-n-*propyl*)*benzidine*	112	Plates	E	$C_{24}H_{32}N_2Cl_4$	58·6	6·6	5·8	58·8	6·6	5·7
NN-*Di*-(2-*hydroxy*-n-*propyl*)-p-*aminostilbene*	132	Short needles	C	$C_{20}H_{25}O_2N$	77·2	7·9	—	77·1	8·1	—
NN-*Di*-2-(*chloro*-n-*propyl*)-p-*aminostilbene*	93	Short needles	E	$C_{20}H_{23}NCl_2$	67·2	6·6	—	67·0	6·5	—
α-*Naphthyldi*-(2-*hydroxy*-n-*propyl*)*amine*	134—136	Small prisms	C	$C_{16}H_{21}O_2N$	73·9	8·2	—	74·1	8·2	—
α-*Naphthyldi*-(2-*chloro*-n-*propyl*)*amine*	—	(Oil)	—	$C_{16}H_{19}NCl_2$	65·0 (Cl = 23·8)	6·4	—	64·9 (Cl = 23·9)	6·5	—
β-*Naphthyldi*-(2-*hydroxy*-n-*propyl*)*amine A* *	111	Plates	E	$C_{16}H_{21}O_2N$	74·5	8·3	—	74·1	8·2	—
Trinitrobenzene complex thereof *	154—155	Purple needles	C–E	$C_{22}H_{24}O_8N_4$	—	—	11·9	—	—	11·9
β-*Naphthyldi*-(2-*chloro*-n-*propyl*)*amine A*	102	Prisms	D	$C_{16}H_{19}NCl_2$	64·7	6·5	—	64·9	6·5	—
β-*Naphthyldi*-(2-*hydroxy*-n-*propyl*)*amine B* *	100—101	Plates	D	$C_{16}H_{21}O_2N$	73·9	8·3	—	74·1	8·2	—
β-*Naphthyldi*-(2-*chloro*-n-*propyl*)*amine B*	82	Prisms	D	$C_{16}H_{19}NCl_2$	64·6	6·3	—	64·9	6·5	—
NN-*Di*-(3-*hydroxy*-n-*propyl*)*aniline*	60	Plates	C	$C_{12}H_{19}O_2N$	69·0	9·1	—	68·9	9·2	—
NN-*Di*-(3-*chloro*-n-*propyl*)*aniline*	—	(Oil)	—	$C_{12}H_{17}NCl_2$	(Cl = 29·0)			(Cl = 28·8)		
Picrate thereof	129—130	Prisms	C	$C_{18}H_{20}O_7N_4Cl_2$	45·4	4·4	—	45·5	4·3	—
NN-*Di*-(3-*bromo*-n-*propyl*)*aniline*	—	(Oil)	—	$C_{12}H_{17}NBr_2$	(Br = 48·0)			(Br = 47·7)		
Picrate thereof	138	Prisms	C	$C_{18}H_{20}O_7N_4Br_2$	38·5	3·7	—	38·3	3·6	—
NN-*Di*-(3-*iodo*-n-*propyl*)*aniline*	48	Prisms	E	$C_{12}H_{17}NI_2$	33·6 (I = 60·0)	3·9	—	33·6 (I = 59·2)	4·0	—
NN-*Di*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*anisidine*	109—111	Prismatic needles	C	$C_{13}H_{19}O_3NCl_2$	51·1	6·2	—	50·7	6·2	—
NN-*Di*-(2 : 3-*dichloro*-n-*propyl*)-p-*anisidine*	—	(Oil)	—	$C_{13}H_{17}ONCl_4$	(Cl = 41·0)			(Cl = 41·1)		
NNN'N'-*Tetra*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*phenylenediamine*	130	Small needles	C	$C_{18}H_{28}O_4N_2Cl_4$	45·4	5·6	—	45·2	5·9	—

Solvents (*S*) as in Table I.

the molecule will contain two asymmetric carbon atoms and normally a mixture of products is to be expected. Generally the hydroxypropyl derivatives were not obtained in a solid form but it was usually possible to prepare crystalline chloro-compounds : many of these do not melt sharply and thus probably consist of a mixture of stereoisomers. In the case of the product derived from β-naphthylamine two compounds were separated—these are regarded as the racemic and the *meso*-form of β-*naphthyldi*-(2-*chloro*-n-*propyl*)*amine* (I). The possibility that one of these products might be a 1-chloro-2-propyl derivative (II) formed by a different direction of ring opening appears to be ruled out by the preparation of both isomers by chlorinating the hydroxypropyl derivatives obtained when 1-bromopropan-2-ol reacts with β-naphthylamine. Further evidence that both isomers are *n*-propyl derivatives is afforded by the hydrolysis reactions described below.



(I.)



(II.)

Attempts to prepare the 2-chloro*iso*propyl derivative (II) by condensing 2-chloro-1-acetoxypropane with β-naphthylamine have been unsuccessful. It is difficult to introduce two α-substituted alkyl groups on to the nitrogen atom of an arylamine, for example, whereas phenylglycine condenses with chloroacetic acid to give phenyliminodiacetic acid (Vorlander and Mumme, *Ber.*, 1901, **34**, 1647), *N*-β-naphthylalanine ethyl ester would not react with α-bromopropionic ester under any of the conditions tried—the product could have been reduced, either by means of sodium and alcohol or catalytically, to give the required *iso*propyl compound. The α-methyl group of the ethyl ester of β-naphthylalanine probably reduces the reactivity of the amino-nitrogen atom by a steric hindering effect; the ester could not be induced to react with ethylene oxide at a high temperature.

Aniline condenses with 3-chloropropan-1-ol to give a hydroxy-*n*-propyl derivative which on chlorination yields NN-*di*-(3-*chloro*-n-*propyl*)*aniline*. Epichlorohydrin condenses with the more basic aromatic amines affording disubstituted products; for example, Strukov (*Khim. Farm. Prom.*, 1934, No. 2, 11 ; *Chem. Abs.*, 1934, **28**, 5421) describes the reaction with *p*-phenetidine hydrochloride. Similarly *p*-anisidine yields NN-*di*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*anisidine* and this has now been converted into the corresponding 2 : 3-*dichloro*-n-*propyl* derivative. *p*-Phenylenediamine dihydrochloride reacts in aqueous solution to give NNN'N'-*tetra*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*phenylenediamine* which is very sensitive to oxidation ; for example, it gives a deep blue colour with a trace of nitrate ions; it has not been possible to convert this into the 2 : 3-dichloro-derivative.

Several unsuccessful attempts have been made to prepare *NN*-di-(4-chloro-*n*-butyl)aniline. The condensation of 4-chlorobutan-1-ol with aniline on one occasion gave 1-phenylpyrrolidine whilst another experiment gave mainly N-(4-*hydroxy*-n-*butyl*)*aniline*. When this monohydroxy-compound was treated with a further quantity of chlorobutanol in aqueous chalk suspension all the alcohol was converted into tetrahydrofuran and none reacted with the amine. When aniline reacted with 4-chloro-1-acetoxybutane the monohydroxybutyl derivative and acetanilide were the only identifiable products. On the other hand aniline condensed normally with 6-chlorohexan-1-ol and chlorination of the *di*(*hydroxy*-n-*hexyl*) derivative thus obtained afforded NN-*di*-(6-*chloro*-n-*hexyl*)*aniline*.

Contrary to the findings of Brunel (*Ann. Chim.*, 1905, **6**, 200), who stated that *cyclo*hexene oxide would only react with aniline to give a mono-substituted product whatever the proportions or the temperature, we have now obtained NN-*di*-(2-*hydroxy*-1-cyclo*hexyl*)*aniline*, chlorination of which yields the *di*-(2-*chloro*-1-cyclo*hexyl*) derivative.

Table III shows the extent of the hydrolysis of a selection of the new arylhalogenoalkylamines in unbuffered aqueous acetone solutions under the standard conditions already described (Part I). The more insoluble compounds had to be hydrolysed at higher dilutions than in the standard procedure and the figures are not strictly comparable though the deviation is relatively small and the effects of the various structural modifications are readily apparent.

The higher rate of hydrolysis of the chloroethyl groups in *NN'*-dimethyl-*NN'*-di-(2-chloroethyl)-*oo'*-diaminodiphenyl as compared with those in *NNN'N'*-tetra-(2-chloroethyl)-*oo'*-diaminodiphenyl confirms the finding that in *NN*-di-(2-chloroethyl) derivatives the mutual effect of the chlorine atoms is to decrease the negative charge on each. The ratio of the rates of hydrolysis for the diphenyl compounds (22 : 56) is almost identical with that previously found for the corresponding aniline derivatives (20 : 58).

TABLE III.

Compound (0·5 millimoles)	Vol. of acetone : water (ml.)	% Hydrolysis in 30 mins. at 66°
NN-Di-(2-chloroethyl)-*p-tert.*-butylaniline	25 : 25	29
Ethyl *NN*-di-(2-chloroethyl)-*p*-aminobenzoate	25 : 25	1·5
N'-Acetyl-*NN*-di-(2-chloroethyl)-*p*-phenylenediamine	25 : 25	41
p-Chloro-*NN*-di-(2-bromoethyl)aniline	25 : 25	66
o-Xenyldi-(2-chloroethyl)amine	50 : 50	31
o-Xenyldi-(2-bromomethyl)amine	50 : 50	94
p-Xenyldi-(2-chloroethyl)amine	50 : 50	12
p-Xenyldi-(2-bromoethyl)amine	50 : 50	70
NN'-Dimethyl-*NN'*-di-(2-chloroethyl)-*oo'*-diaminodiphenyl	35 : 35	56
NNN'N'-Tetra-(2-chloroethyl)-*oo'*-diaminodiphenyl	35 : 35	22
N-Ethyl-*N*-(2-chloro-*n*-propyl)aniline (as picrate)	60 : 60	99
NN-Di-(2-chloro-*n*-propyl)aniline	25 : 25	90
α-Naphthyldi-(2-chloro-*n*-propyl)amine	35 : 35	96
β-Naphthyldi-(2-chloro-*n*-propyl)amine A	35 : 35	82
β-Naphthyldi-(2-chloro-*n*-propyl)amine B	35 : 35	88
NN-Di-(2-chloro-*n*-propyl)-*p*-anisidine	25 : 25	100
p-Chloro-*NN*-di-(2-chloro-*n*-propyl)aniline	30 : 30	64
p-Xenyldi-(2-chloro-*n*-propyl)amine	50 : 50	85
p-Xenyldi-(2-bromo-*n*-propyl)amine	50 : 50	100
NN-Di-(3-chloro-2-hydroxy-*n*-propyl)-*p*-anisidine	25 : 25	4 (8 in 120 mins.)
NN-Di-(2 : 3-dichloro-*n*-propyl)-*p*-anisidine	25 : 25	34
NN-Di-(3-chloro-*n*-propyl)aniline	25 : 25	(1 in 60 mins.) (3 in 120 mins.) (16 in 360 mins.)
NN-Di-(3-bromo-*n*-propyl)aniline	40 : 40	9
NN-Di-(3-iodo-*n*-propyl)aniline	50 : 50	23

All the 2-chloro-*n*-propyl compounds hydrolyse much faster than the corresponding 2-chloroethyl derivatives. The effect of placing a methyl group on the 2-carbon atom, thus making the compounds secondary chloro-derivatives, has a far greater effect on the activity of the halogen atom than any substitution in the aromatic nucleus. Nevertheless the variation in velocity of reaction in the substituted *NN*-di-(2-chloro-*n*-propyl)anilines is still discernible as follows :

$$p\text{-MeO} > \text{H} > p\text{-Ph} > p\text{-Cl}$$

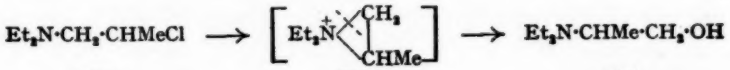
The two *NN*-di-(2-chloro-*n*-propyl)-β-naphthylamines have a similar high rate of hydrolysis; it is doubtful whether a 2-chloro*iso*propyl derivative, which does not contain a secondary chlorine atom, would hydrolyse at this greatly increased rate. This evidence would seem to confirm the formulation of both the naphthylamine compounds as (I).

Whilst the introduction of a 2-methyl group into *NN*-di-(2-chloroethyl)-*p*-anisidine (58% hydrolysed under the standard conditions) has the expected activating effect on the chlorine atoms, the introduction of a 2-chloromethyl group reduces the activity of the original halogen atom even though this atom is now secondary. This is another instance of the mutual effect of chlorine atoms reducing the negative charge on each other and hence their reactivity.

Increasing the distance of the chlorine atom from the nitrogen atom has the expected effect of reducing the rate of hydrolysis, thus the chlorine atoms in *NN*-di-(3-chloro-*n*-propyl)- and *NN*-di-(6-chloro-*n*-hexyl)-aniline are not appreciably hydrolysed under the standard conditions.

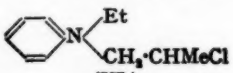
In Part I it was stated that the course of the hydrolysis of *NN*-di-(2-bromoethyl) and *NN*-di-(2-iodoethyl) compounds was complex and appeared to resemble that of the aliphatic " nitrogen-mustards." This conclusion was suggested by the fact that, during the hydrolysis, halide ions seemed to be liberated at a greater rate than hydrogen ions : this indicated the production of quaternary nitrogen atoms in the solution as is the case with the aliphatic compounds. It has since been established that the rate of elimination of halide ions and hydrogen ions is practically identical in the hydrolyses of the bromo- and iodo-derivatives. The higher values for the ionic halogen previously obtained were due to the fact that these compounds hydrolyse quite rapidly even in the cold in the presence of silver nitrate—it has now been established that the increased rate of hydrolysis is caused by the precipitation of halide ions which were previously able to convert some of the carbonium ion (see below) back into the alkyl halide. This effect is most marked in the case of the iodo-compounds but may also be discerned by a drifting end point in the titration of the more rapidly hydrolysed bromo-derivatives. Rapid titration of a well-cooled solution indicates that the halide and hydrogen ion titres are almost identical.

There is good evidence for the existence of ethyleneiminium ions in aqueous solution of the aliphatic chloroalkylamines (Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, 1946, **11**, 518; Hanby, Hartley, Powell, and Rydon, *J.*, 1947, 519). Briefly the existence of these ions is based on (*a*) the rapid elimination, in such solutions, of one equivalent of chloride ion but only traces of hydrogen ion; (*b*) the rapid reaction of the solution with sodium thiosulphate—this reaction is considered to be due to the presence of an ethyleneiminium ion and the so-called instantaneous thiosulphate titre is used as a measure of the concentration of this ion; (*c*) the re-arrangement during hydrolysis of (III) to (V) which is readily interpreted if the ion (IV) is an intermediate and that subsequent re-opening of the ring occurs in a different direction from its formation (S. D. Ross, *J. Amer. Chem. Soc.*, 1947, **69**, 2982).

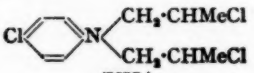


(III.) (IV.) (V.)

There is no such evidence for the existence of an ion of this type during the hydrolysis of the aromatic nitrogen mustards since (*a*) the rates of production of halide and of hydrogen ions are at all times equal; (*b*) the instantaneous thiosulphate titre is negligible; (*c*) compounds (VI) and (VII) have been shown to hydrolyse without change in structure.



(VI.)

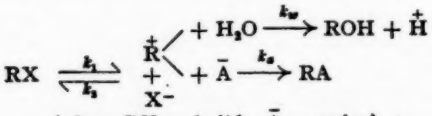


(VII.)

The formation of ethyleneiminium ions and cyclic dimers involves internal or mutual quaternisation. Such quaternisation would appear to be less likely in the case of the feebly basic aromatic derivatives and no dimers have been isolated as yet. It has also proved impossible to prepare quaternary salts by heating any arylhalogenoamine with methyl iodide.

It is fully realised that the evidence presented here only indicates that there can never be any appreciable concentration of an ethyleneimonium ion in aqueous acetone solutions but it does not entirely rule out the possibility of the transitory existence of such ions particularly in wholly aqueous solutions which cannot readily be studied on account of the low water solubility of the compounds.

The relative reactivity of arylhalogenoalkylamines with the various ions and groups likely to be encountered in cellular fluids is of considerable biological significance. The effect of adding salts of organic acids to hydrolysing solutions of the halides has been studied. It was shown in Part I that these hydrolyses proceed by an S_N1 mechanism, and in the presence of an added anion the course of the reaction can be represented as



(where RX = halide, $\bar{A}$ = anion).

The proportion of ROH and RA formed will depend on the magnitude of the rate constants k_w and k_a. The extent of the re-formation of RX (the arylhalogenoalkylamine) will not affect the ratio of the amounts of end products since the halide formed eventually re-ionises and is distributed between the added anion and water. In the earlier experiments on the hydrolysis of the halides in aqueous acetone the sodium hydroxide titre measured the extent of the reaction of $\overset{+}{R}$ with water and the silver nitrate titre measured the extent of the ionisation of the halide. The identity of these two values showed that all the $\overset{+}{R}$ reacted with water and none was involved in quaternary-salt formation. In the presence of added anions these two values will no longer be identical since the reaction of $\overset{+}{R}$ with the anion no longer leads to the production of titratable acid. It can be seen that the extent of the formation of ROH is still measured by the sodium hydroxide titre and the extent of the formation of RA by the difference in the sodium hydroxide and silver nitrate titres. The results obtained in some preliminary experiments made by adding sodium acetate to solutions in which β-naphthyldi-(2-chloroethyl)amine was hydrolysing are shown in Table IV. The ratio of the amounts of ROAc and ROH formed in this experiment

TABLE IV.

Hydrolysis of β-naphthyldi-(2-chloroethyl)amine at 66°.

A, 2 Millimols of amine dissolved in 100 c.c. each of acetone and water (c = 0·01M.). *B*, As *A* with the addition of 40 millimols of sodium acetate (c = 0·20M.).

	*A.**		*B.**		
Time, hours	$\overset{+}{H}$, %	$\overset{-}{Cl}$, %	$\overset{+}{H}$, %	$\overset{-}{Cl}$, %	$\overset{-}{Cl}$, % − $\overset{+}{H}$, %
½	13	13·25	1·3	13	11·7
1	20·75	21·0	2·2	23·3	21·1
4	49·7	49·7	6·5	65·3	58·8

* Based on the replacement of two chlorine atoms.

are: after ½ hour, 9·0; after 1 hour 9·6; after 4 hours 9·1. If this ratio is divided by the concentration of the acetate one obtains a figure which is practically identical with the "competition factor" described by Ogston (*Biochem. Soc. Symposium* No. 2, p. 2). This factor is such that its reciprocal gives the concentration at which the anion must be present—in our experiments in a mixture of equal volumes of acetone and water—so that half of the halide shall react with the anion. From Table IV it can be deduced that at a concentration of 0·2M. the competition factor of the acetate ion is 45·5 (based on the 4-hour titration figures which can be measured with greater accuracy). It is intended to compile a table of competition factors for the arylhalogenoalkylamines similar to that given by Ogston (*loc. cit.*) for di-(2-chloroethyl) sulphide. It will be necessary to examine the effect of varying the pH on the rate of hydrolysis of these halides since acid is produced and salts of different anions will buffer the solutions to different extents. It is, however, possible at the moment to compare the competition factors of different halides with a single anion; a few values for the acetate ion are given in Table V.

TABLE V.

Compound	Competition factor for acetate ions ([NaOAc] = 0·2M. in 1 : 1 acetone–water)	% Hydrolysis in ½ hr. at 66° in acetone–water (Part I)
β-Naphthyldi-(2-chloroethyl)amine	47	15
β-Naphthyldi-(2-bromoethyl)amine	50	80
NN-Di-(2-chloroethyl)-*p*-toluidine	52	38
NN-Di-(2-chloroethyl)-*p*-anisidine	57	58
N-Ethyl-*N*-2-chloroethylaniline	57	58
β-Naphthyldi-(2-chloro-*n*-propyl)amine A	14	82
β-Naphthyldi-(2-chloro-*n*-propyl)amine B	14	88
NN-Di(2-chloro-*n*-propyl)aniline	13	90
NN-Di-(2-chloro-*n*-propyl)-*p*-anisidine	15	100

The values of the competition factor of a chloroethylamine do not vary a great deal from compound to compound even though the rates of hydrolysis of the derivatives vary considerably. It is particularly interesting to note that in the case of the two β-naphthyl-halogenoethylamines the factor is almost the same for the chloro- and bromo-compounds; this is to be expected if an S_N1 mechanism is operating, for the ratio of the end products will depend on the carbonium ion and should be independent of the halogen (compare Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 1005). The fact that the aniline derivative which contains a single chloroethyl group has practically the same factor as the disubstituted compounds, supports the view that each chloroethyl group can react independently. The dependence of biological activity on the presence of two halogenoalkyl groups would not appear to be connected with any mutual effect on their ability to react with organic anions.

The substitution of the 2-carbon atom in the halogenoethyl compounds with a methyl group, besides having a large effect on the rate of hydrolysis of the derivative, also greatly influences the competition factor, for under comparable conditions the chloro-*n*-propylamines will react with about one-quarter to one-third as much acetate ion as the chloroethylamines. Further, the two isomeric β-naphthyl(chloro-*n*-propyl)amines have identical factors—another indication that they are stereoisomers and not structural isomers.

There is a further difference between the aliphatic and the aromatic chloroethylamines, namely, in their hydrolyses in the presence of acetate ions. Fruton, Stein, and Bergmann (*J. Org. Chem.*, 1946, **11**, 567) state that there is no evidence of ester formation when methyl- or ethyl-di-(2-chloroethyl)amine hydrolyses in the presence of sodium acetate. This they

ascribe to the rapid hydrolysis of any ester that might be formed. It has been established that *β-naphthyldi-(2-acetoxyethyl)amine* is not hydrolysed under the conditions of the determination of the competition factor. This difference between the chloroalkylamines suggests that the aromatic derivatives would form more stable products when they interact with carboxyl groups in biological material.

The structural requirements for activity in the halogenoalkylamines—two reactive groups in the molecule—suggested that other compounds containing two groupings capable of reacting with functional centres of biological systems might be effective as cytotoxic agents. It is well known that iodoacetyl groups react with thiols even more readily than the sulphur and nitrogen mustards and so it was considered of interest to prepare and examine NN′-*di(iodoacetyl)-o-phenylenediamine*. Although this compound does not appreciably inhibit the growth of the transplanted Walker tumour under our conditions of test it does produce similar effects on chromosomes (*e.g.*, breakage and anaphase bridging in epithelial cells of the newt, *Triturus palmatus*) to those obtained with the nitrogen-mustards (private communication from Mr. A. Loveless of this Institute). This result suggests that it would be desirable to test other compounds containing two reactive groups in the molecule: this line of approach is now being pursued.

Experimental.

Preparation of Arylhalogenoethylamines.—For the preparation of the hydroxyethyl compounds it has been found preferable to use Method A (Part I), heating the sealed tubes to 150° in all cases. Conversion into the halogeno-derivatives was carried out as before; the yield of chloro-compound was generally about 50%, and lower yields of bromo- and iodo-compounds were obtained. During the bromination of the hydroxy-compounds with phosphorus tribromide an orange complex has been encountered on several occasions and unless this is decomposed by shaking it with a solution of sodium hydrogen carbonate low yields of the bromoethyl derivatives are obtained. It is not possible to prepare the iodo-compounds by heating the chloroalkylamines with sodium iodide in acetone solution since the reaction is so slow that some hydrolysis of the iodide occurs during the preparation. Even when the bromo-derivatives are converted into iodides it is advisable to dry the sodium iodide and the acetone used in order to minimise the loss of the readily hydrolysed iodo-compounds.

NN-*Di-(2-chloroethyl)-p-aminobenzoic Acid.*—Ethyl *NN*-di-(2-chloroethyl)-*p*-aminobenzoate (1 g., prepared by chlorinating the product obtained by the action of ethylene oxide on ethyl *p*-aminobenzoate) was heated under reflux with concentrated hydrochloric acid for 15 minutes. Gradually the acid separated in a crystalline form, which gave needles, m. p. 171·5°, undepressed by admixture with a specimen prepared as described by Ross (*loc. cit.*), when crystallised from aqueous methanol. The *methyl* ester, formed by the action of ethereal diazomethane on the acid, melted at 58° (plates from light petroleum, b. p. 60—80°).

NN-*Di-(2-hydroxyethyl)-p-aminoazobenzene.*—A solution of the diazonium salt prepared from aniline (1·8 c.c.), concentrated hydrochloric acid (6 c.c.), water (20 c.c.), and sodium nitrite (1·4 g.) was added to a cooled solution of *NN*-di-(2-hydroxyethyl)aniline (3·6 g.) in methanol (10 c.c.). After ½ hour the deep red solution was basified with ammonium hydroxide and extracted with ether. Concentration of the dried extract by evaporation gave the *azo*-compound which crystallised from benzene in deep-orange plates, m. p. 133—135°.

NN-*Di-(2-chloroethyl)-p-aminoazobenzene.*—(*a*) A solution of benzenediazonium chloride, prepared as above, was added to a solution of *NN*-di-(2-chloroethyl)aniline (4·4 g.) in ethanol (100 c.c.). The mixture was shaken for ½ hour and then diluted with water (200 c.c.). The oily precipitate gradually solidified and was dissolved in benzene and the solution was passed down a column of activated alumina which was then washed with fresh benzene. Evaporation of the orange eluates afforded the *chloro*-compound, m.p. 73—75°, which formed large thin orange plates from light petroleum (b. p. 40—60°) in which it is very soluble.

(*b*) The hydroxy-azo-derivative (2 g.), phosphorus oxychloride (5 c.c.), and benzene (30 c.c.) were heated under reflux for ½ hour. The cooled mixture was poured on to ice and the benzene layer was dried and passed through a column of alumina. The product had m. p. 72—74°, not depressed by material prepared by method (*a*). The azo-compound yields a light orange solution in alcohol the colour of which changes to a deep crimson when concentrated hydrochloric acid is added.

p′-*Nitro*-NN-*di-(2-chloroethyl)-p-aminoazobenzene.*—A solution of the diazonium salt prepared from *p*-nitroaniline (7 g.), concentrated hydrochloric acid (10 c.c.), water (150 c.c.), and sodium nitrite (3·5 g.) was added to a solution of *NN*-di-(2-chloroethyl)aniline (11 g.) in ethanol (250 c.c.). The red precipitate was collected, dried, and crystallised from acetone; it formed large, deep red glistening plates, m. p. 166—167°. The orange-red alcoholic solution of the azo-compound assumes an intense crimson colour when an excess of concentrated hydrochloric acid is added.

NN-*Di-(2-chloroethyl)-p-nitrosoaniline.*—*NN*-Di-(2-chloroethyl)aniline (54 g.) was dissolved in a warm mixture of concentrated hydrochloric acid (105 c.c.) and water (100 c.c.). After being cooled to 5° the solution was vigorously stirred and a solution of sodium nitrite (18 g.) in water (50 c.c.) was added at such a rate that the temperature remained at 5—7°. After the addition, which took one hour, the mixture was stirred for a further 20 minutes and then ether (1 l.) and water (1 l.) were added. The aqueous layer was separated and re-extracted twice with ether (1 l.). The dried extracts deposited the *nitroso*-derivative as deep green plates (49 g.), m. p. 79—80°, when evaporated.

NN-*Di-(2-chloroethyl)-p-phenylenediamine.*—The nitrosoamine (2·0 g.) was dissolved in concentrated hydrochloric acid (40 c.c.) and stannous chloride crystals (3 g.) were gradually added with constant shaking and cooling. The stannichloride of the amine separated in the form of a buff granular precipitate;

this was collected by filtration and washed with a little concentrated hydrochloric acid. The product was dissolved in water, treated with a slight excess of N-sodium hydroxide, and rapidly extracted with ether. Hydrogen chloride was passed into the dried ethereal solution until plates of the *monohydrochloride* of the amine separated. The amount of gas passed into the solution must be only slightly in excess of the theoretical quantity or the base is thrown out as an oil which is probably the dihydrochloride. The monohydrochloride was dissolved in a small amount of methanol and, on the addition of ether to the filtered solution, the salt was obtained as large colourless plates, m. p. 250—260° (decomp.). The monohydrochloride is water soluble (20 mg. per 1 c.c. at 20°). One drop of this solution placed on the skin will produce a blister of approximately one inch in diameter after 24 hours. As in the case of the aliphatic nitrogen-mustards such blisters are slow to heal.

Esters of NN*-Di-*(2*-chloroethyl*)-p-*phenylenediamine.*—(*a*) The monohydrochloride (1 g.) was dissolved in water (10 c.c.) and the solution was saturated with sodium acetate. A slight excess of acetic anhydride was added dropwise to the well-cooled and shaken solution. The solid *acetyl* derivative which separated was collected and dissolved in benzene. On the addition of light petroleum (b. p. 60—80°) to the concentrated solution flattened needles, m. p. 124—126°, were deposited.

(*b*) A slight excess of benzoyl chloride was added to a cooled, stirred mixture of the monohydrochloride (1 g.) in water (50 c.c.) containing sodium carbonate (5 g.). When all the benzoyl chloride had reacted the product was extracted with benzene, and the dried extract was allowed to percolate through a short column of alumina. The *benzoyl* derivative was obtained as fine colourless needles, m. p. 164—165°, on concentrating the eluates.

Reduction of oo′*-Dinitrodiphenyl.*—(*a*) *oo′*-Dinitrodiphenyl (6·1 g., prepared by the method of Shaw and Turner, *J.*, 1933, 139), Raney nickel catalyst (2 g.), and ethanol (100 c.c.) were shaken in an atmosphere of hydrogen until the uptake of gas ceased (8 hours). When half of the theoretical amount of hydrogen had been absorbed a mass of fine white needles separated but these re-dissolved as more gas was taken up. On concentrating the filtered solution yellow prisms of benzcinnoline, m. p. 156—158°, were deposited (Found : C, 80·2; H, 4·6. Calc. for $C_{12}H_8N_2$: C, 80·0; H, 4·5%).

(*b*) Dinitrodiphenyl (43 g.), stannous chloride crystals (240 g.), concentrated hydrochloric acid (210 c.c.), and ethanol (100 c.c.) were heated on a steam-bath until a vigorous reaction occurred. This was controlled by cooling, and when all the material had dissolved the mixture was heated on steam for a further ½ hour. An excess of sodium hydroxide was then added and the product extracted with ether. The diamine formed prisms, m. p. 77—78°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 78·0; H, 6·6. Calc. for $C_{12}H_{12}N_2$: C, 78·2; H, 6·6%).

oo′*-Di-*(N*-methyltoluene-*p*-sulphonamido)diphenyl.*—Toluene-*p*-sulphonyl chloride (40 g.) was gradually added to a solution of diaminodiphenyl (18·4 g.) in dry pyridine (40 c.c.). After the initial reaction had moderated the mixture was heated for one hour on a steam-bath. The *bistoluene-*p*-sulphonamide* was precipitated by the addition of water; after crystallisation from methanol it melted at 147—149° (Found : C, 63·6; H, 4·8. $C_{26}H_{24}O_4N_2S_2$ requires C, 63·4; H, 4·9%). A solution of the sulphonamide (18 g.) in water (65 c.c.) and N-sodium hydroxide (65 c.c.) was treated with dimethyl sulphate (3·1 c.c.). After ½ hour's stirring N-sodium hydroxide (50 c.c.) and dimethyl sulphate (2·5 c.c.) were added and the reaction was allowed to continue until the resinous precipitate of oo′*-di-*(N*-methyltoluene-*p*-sulphonamido)diphenyl* solidified. After several crystallisations from acetone, large prisms, m. p. 192—193°, were obtained (Found : C, 64·5; H, 5·4. $C_{38}H_{36}O_4N_2S_2$ requires C, 64·6; H, 5·4%).

NN′*-Dimethyl-*oo′*-diaminodiphenyl.*—The sulphonamide (45 g.) was heated at 160° for 5 minutes with sulphuric acid (150 c.c. of 80% acid, prepared by mixing 3 vols. of acid with 1 vol. of water). After cooling, the solution was poured into water, basified with sodium hydroxide, and the *diamine* which separated was crystallised from acetone–methanol. It formed prismatic needles, m. p. 154—156° (Found : C, 78·7; H, 7·6. $C_{14}H_{16}N_2$ requires C, 79·2; H, 7·6%). The diamine was converted successively into the *di-*(2*-hydroxyethyl*) and the *di-*(2*-chloroethyl*) derivative. The latter is very soluble in light petroleum (b. p. 40—60°) and solutions have to be cooled in a freezing mixture in order to obtain reasonable yields on recrystallisation.

Preparation of 2*-Chloro-*n*-propylamines.*—The arylamine (0·1 mol.) and propylene oxide (0·22 mol.; 15 c.c.) were heated in a sealed tube at 150° for 16 hours. When ethylene oxide is used it is very necessary to use exactly theoretical quantities of reactants to prevent side reactions but it is possible to use an excess of propylene oxide (compare Hanby and Rydon, *J.*, 1947, 514). Whenever possible the reaction product was crystallised from benzene or light petroleum (b. p. 60—80°). If any difficulty was encountered, the crude hydroxypropyl compound was chlorinated as described in Part I (preparation of chloroethylamines; Method B). Better results have generally been obtained when the hydroxy-derivative was first dissolved in an amount of dry benzene equal in volume to that of the phosphorus oxychloride used. The 2-chloropropylamines were usually submitted to a chromatographic purification and crystallised from light petroleum (b. p. 40—60°).

β-Naphthyldi-(2*-chloro-*n*-propyl*)*amine* A *and* B.—(*a*) A mixture of the chloropropylamines was prepared from β-naphthylamine exactly as described above; the crude material melted at 84—90°. Repeated crystallisation from light petroleum (b. p. 40—60°) eventually gave the less soluble derivative designated *β-naphthyldi*(*chloropropyl*)*amine* A, m. p. 102°; the more soluble *compound* B, m. p. 82°, was obtained by fractional crystallisation of the mother liquors.

(*b*) β-Naphthylamine (14·3 g.), 1-bromopropan-2-ol (41·7 g.), calcium carbonate (15 g.), and water (20 c.c.) were heated under reflux for 24 hours. The cooled, filtered solution was extracted with benzene and the dried extract was passed through a column of alumina. This column was washed with fresh benzene until all the unchanged naphthylamine had been removed and the eluates were colourless. Further elution of the column with chloroform gave a dark oil (5 g.) which was chlorinated and the product was crystallised from light petroleum. Isomer *A*, m. p. 102°, was readily obtained in low yield but in order to obtain the lower-melting isomer the mother liquors were passed through a column of alumina. The first eluates yielded solid, m. p. 82°, unchanged by crystallisation. It is not possible to identify the isomers by a mixed melting point test since one isomer barely depresses the melting point of the other—most mixtures melt at intermediate temperatures.

Hydrolysis of the Naphthylchloropropylamines.—The chloro-compound (1 g.) and acetone (200 c.c.) containing sodium hydroxide (3·4 c.c. of 2N.) were heated under reflux for 3 hours. After removal of the acetone under reduced pressure the solution was saturated with sodium chloride and extracted several times with ether. The dried ethereal extracts were evaporated and the residue crystallised from light petroleum. The characteristics of the hydroxy-compounds are given in Table II.

Hydrolysis of N-*Ethyl*-N-(2-*chloro*-n-*propyl*)*aniline Picrate.*—The picrate (432 mg.) was dissolved in acetone (60 c.c.) and the solution was titrated with N/10-sodium hydroxide using phenolphthalein as indicator: 10·1 c.c. of alkali were required. Water (50 c.c.) was added and the mixture was heated under reflux for 30 minutes. Titration with alkali indicated that hydrolysis was complete. The hydroxy-compound was isolated as above and converted into the picrate, m. p. 123—124°, undepressed by admixture with picrate of the compound obtained by the reaction of ethylaniline with propylene oxide.

Hydrolysis of p-*Chloro*-NN-*di*-(2-*chloro*-n-*propyl*)*aniline.*—The chloropropylamine (280 mg.) was heated under reflux for ½ hour in water (70 c.c.) and acetone (70 c.c.). Titration of the acidity produced indicated that 65% of the halide had hydrolysed. The hydroxy-compound was isolated as before and crystallised from light petroleum (b. p. 60—80°). It melted at 104—106° and was identical with the product originally obtained by the action of propylene oxide on *p*-chloroaniline.

Attempted Reaction of N-*β*-*Naphthylalanine Ethyl Ester.*—(a) *With α-bromopropionic ester.* *N*-*β*-Naphthylalanine ethyl ester (0·1 mol.), ethyl α-bromopropionate (0·1 mol.), and anhydrous sodium acetate (0·15 mol.) were heated for 5 hours at 180—200°. Only unchanged material could be isolated from the reaction mixture.

(b) *With ethylene oxide.* The alanine derivative (0·1 mol.) was heated with ethylene oxide (0·1 mol.; 5 c.c.) in a sealed tube at 160° for 12 hours. Again, only unchanged ester could be isolated.

NN-*Di*-(3-*hydroxy*-n-*propyl*)- *and* NN-*Di*-(6-*hydroxy*-n-*hexyl*)-*aniline.*—These hydroxyalkyl derivatives were obtained by heating aniline (0·5 mol.), 3-chloropropan-1-ol or 6-chlorohexan-1-ol (1·5 mols.), calcium carbonate (0·5 mol.), and water (500 c.c.) under reflux with vigorous stirring until all the chalk had dissolved (30 hours). The *hydroxyhexyl* derivative was obtained as an oil which distilled at about 200°/0·01 mm. (oil-bath temperature—some decomposition occurred and a higher-boiling fraction was left in the flask) (Found: C, 73·3; H, 10·7. $C_{18}H_{31}O_2N$ requires C, 73·7; H, 10·6%); it formed a *bis*-3 : 5-*dinitrobenzoate*, m. p. 112°, crimson needles from ethyl acetate–ethanol (Found: C, 56·5; H, 5·4. $C_{32}H_{35}O_{12}N_5$ requires C, 56·4; H, 5·2%).

NN-*Di*-(6-*chloro*-n-*hexyl*)*aniline* was obtained as a colourless oil (Found: C, 65·6; H, 8·7. $C_{18}H_{29}NCl_2$ requires C, 65·4; H, 8·9%).

The Condensation of 4-*Chlorobutan*-1-*ol with Aniline.*—Aniline (18·6 g.), 4-chlorobutan-1-ol (65 g.), calcium carbonate (80 g.), and water (100 c.c.) were heated under reflux with vigorous stirring. When an oil was observed to be condensing the water in the condenser was stopped and the oil was collected at 64—66° and was shown to be tetrahydrofuran. More chlorobutanol (30 c.c.) was added and the heating was continued for 6 hours. Altogether 25 g. of tetrahydrofuran were collected. The cooled mixture was extracted with ether and the dried extract was distilled.

N-(4-*Hydroxy*-n-*butyl*)*aniline* was collected at 125—135°/1 mm. (Found: C, 72·5; H, 8·6. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1%). The *trinitrobenzene* complex formed reddish-brown needles, m. p. 73—74°, from benzene–*cyclo*hexane (Found: N, 14·6. $C_{16}H_{18}O_7N_4$ requires N, 14·8%).

Hydroxybutylaniline (7·3 g.), 4-chlorobutan-1-ol (14·4 g.), calcium carbonate (15 g.), and water (20 c.c.) were heated with stirring for four hours. During this time tetrahydrofuran was evolved. Only unchanged monohydroxybutylaniline could be isolated from the reaction mixture.

NN-*Di*-(2 : 3-*dichloro*-n-*propyl*)-p-*anisidine.*—*p*-Anisidine (6·15 g.) and epichlorohydrin (8 c.c.) were warmed together until solution was complete and then kept at room temperature for 2 days. The solid *product* crystallised from benzene as prismatic needles, m. p. 109—111°. Chlorination of the hydroxy-derivative with phosphorus oxychloride afforded a yellow oil which gave good analytical figures after a chromatographic purification.

NNN'N'-*Tetra*-(3-*chloro*-2-*hydroxy*-n-*propyl*)-p-*phenylenediamine.*—*p*-Phenylenediamine (5·4 g.), epichlorohydrin (16 c.c.), concentrated hydrochloric acid (10 c.c.), and water (40 c.c.) were shaken at room temperature for 30 hours. The purple solid which separated was dried and crystallised twice from benzene as small bluish needles, m. p. 130°. The blue colour is probably due to the presence of an oxidation product for when a solution of the hydroxy-compound is treated with traces of oxidant (*e.g.* nitrates, ferric chloride, or hydrogen peroxide) an intense blue colour develops. All attempts to chlorinate this substance gave only dark resins.

NN-*Di*-(2-*hydroxy*-1-*cyclo*hexyl)*aniline.*—Aniline (9·3 g.), *cyclo*hexene oxide (19·6 g.), and benzene (10 c.c.) were heated in a sealed tube at 185° for 24 hours. After the excess of *cyclo*hexene oxide and benzene had been removed by evaporation NN-*di*-(2-*hydroxy*-1-*cyclo*hexyl)*aniline* was crystallised from benzene as felted needles (3·5 g.), m. p. 175—177° (Found: C, 74·8; H, 9·3; N, 4·7. $C_{18}H_{27}O_2N$ requires C, 74·7; H, 9·4; N, 4·8%).

NN-*Di*-(2-*chloro*-1-*cyclo*hexyl)*aniline.*—The above hydroxy-compound (1 g.), phosphorus oxychloride (1 c.c.), and benzene (10 c.c.) were heated under reflux for 2 hours. The mixture was poured on to ice, the dried benzene layer was evaporated, and the residue dissolved in light petroleum (b. p. 60—80°). This solution was shaken with a little activated alumina, filtered, and evaporated. The *chloro*-compound thus obtained crystallised from pentane as small prisms, m. p. 97—99° (Found: C, 66·2; H, 7·7; N, 4·6. $C_{18}H_{25}NCl_2$ requires C, 66·2; H, 7·7; N, 4·3%).

NN'-*Di*-(*chloroacetyl*)- *and* -(*iodoacetyl*)-o-*phenylenediamine.*—Finely powdered *o*-phenylenediamine (10·8 g.) was suspended in water (100 c.c.) and the mixture was cooled and stirred whilst chloroacetyl chloride (14 c.c.) was added dropwise. After being kept for ½ hour the dark product was collected and dried, then mixed with charcoal and extracted with acetone in a Soxhlet apparatus. The pink extract was recrystallised from acetone giving colourless flattened needles of the *chloroacetyl* compound, m. p. 204° (Found: C, 45·7; H, 3·9. $C_{10}H_{10}O_2N_2Cl_2$ requires C, 46·0; H, 3·9%). The bischloroacetamide (1 g.), anhydrous sodium iodide (2 g.), and dry acetone (25 c.c.) were heated on a steam-bath for ½ hour. Water was added to dissolve the sodium chloride which had rapidly separated from the solution and, on cooling,

the *iodoacetyl* derivative was deposited. Recrystallisation from methanol gave long felted needles, m. p. 201—202° (Found : C, 26·8, 27·3; H, 2·3, 2·4. $C_{10}H_{10}O_2N_2I_2$ requires C, 27·1; H, 2·3%).

Both halogenoacetyl compounds react with thiophenol in methanol to give a *disulphide*, m. p. 143—144°, needles from aqueous methanol (Found : C, 65·1; H, 5·1. $C_{32}H_{30}O_2N_2S_2$ requires C, 64·7; H, 4·9%).

Attempted Formation of Quaternary Salts.—(*a*) *NN*-Di-(2-hydroxyethyl)aniline was recovered unchanged after being heated under reflux with a large excess of methyl iodide for 8 hours.

(*b*) *NN*-Di-(2-chloroethyl)aniline was also unaffected when heated for 24 hours with an excess of methyl iodide or ethylene dibromide.

Rates of Hydrolysis of Arylhalogenoamines.—(*a*) *In unbuffered solutions.* The rates of hydrolysis at 66° in 1 : 1-acetone–water solutions were determined exactly as in Part I. In the case of the more rapidly hydrolysed halides, particularly the iodo- and bromo-derivatives, it was necessary to cool the solutions in ice before titrating in order to obtain clear end-points in the titration with silver nitrate.

(*b*) *In the presence of sodium acetate* (*determination of competition factor*). Water (100 c.c.) and acetone (100 c.c.) containing sodium acetate (40 millimoles, giving a 0·2M-solution) was neutralised with N/10-sodium hydroxide (phenolphthalein) and heated to boiling point. The arylhalogenoalkylamine (2 millimoles) was then added, and the solution was heated under reflux for the required time. The well cooled solution was titrated first with N/10-alkali and then with N/10-silver nitrate (dichlorofluorescein).

Preparation and Attempted Hydrolysis of β-Naphthyldi-(*2-acetoxyethyl*)*amine.*—β-Naphthyldi-(2-hydroxyethyl)amine (2 g.), acetic anhydride (2 c.c.), and benzene (10 c.c.) were heated on a steam-bath for one hour. After removal of the solvents a solution of the residue in benzene was passed through a column of alumina and the early eluates were concentrated giving the *acetoxy*-compound as a colourless oil (215 mg. of this oil required 13·7 c.c. of N/10-alkali for complete hydrolysis; theory for $C_{18}H_{21}O_4N$ = 13·7 c.c.).

312 Mg. of the compound were heated under reflux with acetone and water (50 c.c. of each) for 3 hours. Approximately 0·2 c.c. of N/10-alkali was required to titrate the acidity produced. Thus the acetate is stable to hot neutral aqueous solutions.

308 Mg. of the acetoxy-derivative were heated under reflux for 3 hours with acetone and water (50 c.c. of each) containing acetic acid (20 c.c.; N/10—this is a considerably higher proportion of acid than is likely to be encountered in the determination of the competition factor). No extra acidity was developed during this heating thus indicating that the acetate is stable under these conditions.

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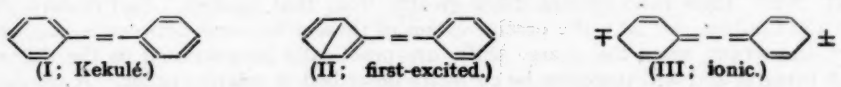
421. *Charge Distribution and Bond Orders in Aminostilbene and Related Molecules.*

By C. A. COULSON and (MISS) J. JACOBS.

Calculations are reported, using the method of molecular orbitals, of the charge distribution and the bond orders in aminostilbene and some related molecules. These calculations relate both to the ground state of the molecule and to its first-excited state. They show the expected alternating character of the equilibrium charge distribution, and the results are interpreted in terms of the particular valence-bond structures (Kekulé, first-excited, ionic) which appear to be most important. The effect of one amino-group in one ring does not extend appreciably into the other ring.

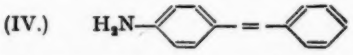
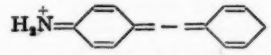
WHEN using the standard representation of a molecule in terms of resonance structures (*e.g.*, Pauling, " Nature of the Chemical Bond," Cornell Univ. Press, 1940) it is usual to introduce unexcited (*i.e.*, Kekulé) structures, first-excited structures, and ionic structures. More excited structures are generally assumed to be negligible. For example, stilbene would conventionally be represented as a resonance hybrid of structures such as (I)—(III). In the lowest molecular energy level which is reached by absorption of light from the ground level, it has usually been supposed that the ionic structures (III) are fairly important; in classical language this



(I; Kekulé.) (II; first-excited.) (III; ionic.)

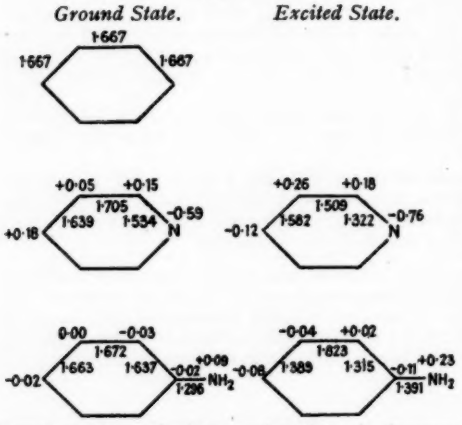
corresponds to an electron oscillating from one end of the molecule to the other and hence being responsible for the intense absorption. In principle, such a description of the molecule is quite

proper; but in practice it suffers from the considerable drawback that there seems at present no satisfactory way of calculating the relative weights of the various types of structure. The situation is even less satisfactory in substituted and heterocyclic molecules. Thus in 4-aminostilbene, in addition to the Kekulé structures (IV), we expect ionic structures such as (V), which are similar to (III) except that the charge on the amino-nitrogen can only be positive. But there is no available estimate of the relative weights of (IV) and (V), though that of (V) in the

(IV.)   (V.)

substituted compound is usually supposed to exceed that of (III) in the unsubstituted. A summary of some evidence is given by Branch and Calvin (" Theory of Organic Chemistry," Prentice-Hall, 1941). In the excited level nothing whatever is known of the weights. Now this molecule and its derivatives have very important biological functions in carcinogenesis (Haddow, Harris, Kon, and Roe, *Phil. Trans.*, 1948, *A*, **241**, 147) which may depend on the charge distribution. For this reason, and because of our ignorance about the relative weights of structures such as those referred to earlier, we have thought it worth while to calculate the charge distribution and bond orders in this and some related molecules, using the method of molecular orbitals. In this method no specific reference is made to any constituent structures such as (IV) or (V), but the results of our calculations allow us to infer which structures are important and which are not, and to estimate approximately their weights. Our calculations are concerned both with the ground level of the molecule and with the first-excited level, as they are described by the method of molecular orbitals. There is no reason to suppose that these molecules are essentially different from other substituted systems of chain type, so that we may expect that the type of answer found for the systems studied in this paper will be found equally in others.

FIG. 1.



Bond orders and charge migrations in benzene, pyridine, and aniline. The bond orders are shown along the various bonds. The figures at the atoms denote the charge distribution, measured in fractions of an electron, relative to a neutral atom; e.g., in the ground state of aniline, the nitrogen atom is deficient in electrons to the extent of 0·09e *and therefore carries a net charge* + 0·09e.

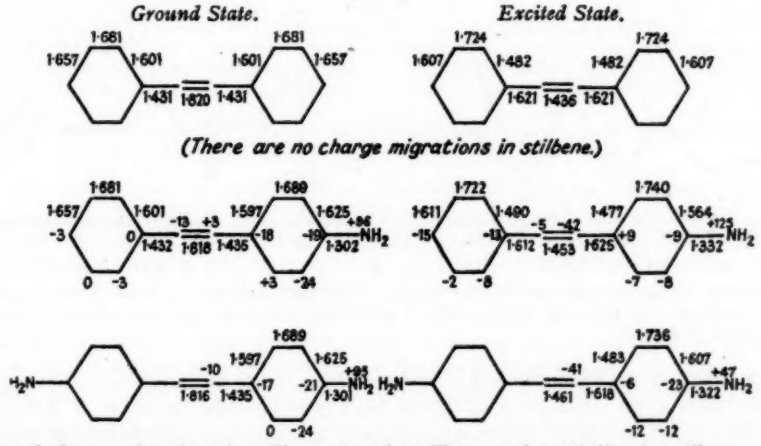
The significance of bond orders in this connection may be seen from the particular example of 4-aminostilbene. If structures such as (V) are important, then not only should there be a negative charge on the 4′-carbon atom, but the two benzene rings should have considerable quinonoid character. This will be revealed by the bond orders: for if the six bonds in these rings have substantially equal orders, we can treat the rings as aromatic, but if the orders of bonds 2–3 and 2′–3′ are higher than the others, the rings are essentially quinonoid.

In making our calculations we have used quite standard technique, which need not therefore be described. It is precisely the same as that used by Longuet-Higgins and Coulson (*Trans. Faraday Soc.*, 1947, **43**, 87) and originally introduced by Wheland and Pauling (*J. Amer. Chem. Soc.*, 1935, **57**, 2086): that is to say, we calculate solely the motion of the π electrons, and we assume (i) that all resonance integrals β, whether between carbon and carbon, or carbon and nitrogen, are equal, (ii) that all overlap integrals S may be neglected, (iii) that the Coulomb integral α_N for a nitrogen is related to α_C for a carbon by the equation $\alpha_N = \alpha_C + 2\beta$, and (iv) that for a carbon atom C′ adjacent to a nitrogen $\alpha_{C'} = \alpha_C + \frac{1}{2}\beta$. It is very probable (Longuet-Higgins and Coulson, this vol., p. 971) that the values 2β and $\frac{1}{2}\beta$ used above are too great, perhaps by as much as a factor of 2 or 3, though, as Wheland has shown (*J. Amer. Chem. Soc.*, 1941, **63**, 2025), their ratio cannot differ greatly from that quoted. Fortunately (Longuet-Higgins and Coulson, *loc. cit.*), the precise values of these differences between α_N, $\alpha_{C'}$, and α_C are not very important, since the charge shifts are practically proportional to the differences of Coulomb integral and will therefore be correctly described in relative order. A similar correct relative sequence may be expected for the bond orders. Thus, when interpreting the charge migration in Figs. 1 and 2, it is safest to treat them as determining relative, rather than absolute,

values. Similarly, the differences between the bond orders shown and the aromatic value 1·667 found for benzene, are likely to be more reliable relatively than absolutely.

Our calculations fall into two groups: (i) the simple series, benzene, pyridine, and aniline; (ii) the larger molecules stilbene, and 4-amino- and 4 : 4′-diamino-stilbene. The results are all shown in Figs. 1 and 2. We have omitted the excited level of benzene from Fig. 1 because, on account of the extremely high symmetry of this molecule, degeneracies appear in the electronic energy levels of a type quite distinct from those found in any of the other molecules. Also, in the case of aniline, the method of molecular orbitals predicts two allowed transitions with approximately equal energies. These transitions are of quite different types; we have therefore chosen that one which appears to us the more plausible and corresponds the more nearly with the transition in the stilbene group, where this ambiguity does not appear. The values in the ground levels of group (i) molecules have already been published (Wheland and Pauling, *loc. cit.*; Longuet-Higgins and Coulson, *loc. cit.*) but are repeated for comparison. All other values in Figs. 1 and 2 are new.

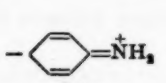
FIG. 2.



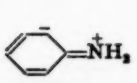
Bond orders and charge migrations in stilbene, 4-aminostilbene, and 4 : 4′-diaminostilbene. Positions not labelled may be found by symmetry. The net charges on the atoms are shown in units of e/1000.

These figures are almost self-explanatory. But in Fig. 1 we notice the essential difference between molecules with the nitrogen atom as part of the ring or as substituent in it. The ground level of aniline is more nearly aromatic (all bond orders = 1·667) than that of pyridine; but on excitation aniline assumes a distinctly quinonoid character, showing the importance of structures such as (VI). Since the charge on the *p*-carbon atom is now twice as great as that on the *o*- or *m*-carbons, we see that (VI) is more important than (VII). The greater importance of both (VI) and (VII) in the excited than in the ground level is revealed by the fact that the $>C=\overset{+}{N}H_2$ bond order increases appreciably on excitation. In pyridine, however, all the bond orders decrease on excitation, and the small amount of quinonoid character present in the ground state is completely removed. In aniline, excitation results in a migration of charge from the nitrogen: in pyridine the migration is on to the nitrogen. It is almost certain that our calculations have exaggerated these effects, so that, for example, excited pyridine is not so polar a molecule as Fig. 1 would suggest. Indeed, comparison of our predicted resonance dipole moments with those inferred from the observed total molecular moment suggests that, in both groups of molecule dealt with here, our calculated charge displacements are about twice too large. But there can be no doubt about the essential difference between these two molecules.

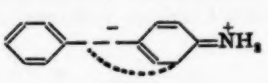
One or two points in Fig. 2 are noteworthy. In all these molecules the excitation appears to reside almost entirely in the central ethylene link, converting $- = -$ into $= - =$. This appears to be almost unaffected by the presence either of one or of two *p*-amino-substituents.



(VI.)



(VII.)

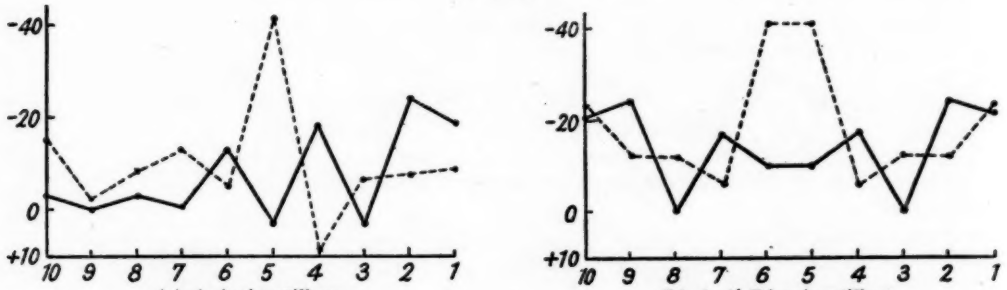


(VIII.)

In the ground state of stilbene there is a little—but only a little—quinonoid character of the kind represented in (III), so we are led to believe that these particular structures are not very important. Conclusions similar to this have already been obtained by B. Pullman (*Bull. Soc. chim.*, 1948, **15**, 533) on other grounds, and may therefore be said now to be quite definite. On excitation there is rather more quinonoid character, and in the amino-compounds the quinonoid character of the substituted ring is greater still. This indicates the importance of structures such as (V) and also (VIII). The apparently great importance of (VIII) in the excited state is quite unexpected, but it seems inevitable if we are to interpret our molecular orbital calculations in terms of structures of the conventional kind.

It will also be noticed that the two amino-groups are practically independent of each other. Thus the charge migrations in the 4 : 4′-compound are very little different from a superposition of the migrations in the 4- and the 4′-compound separately.

FIG. 3.



(a) 4-*Aminostilbene.* (b) 4 : 4′-*Diaminostilbene.*

Charge distribution in the ground and excited states. The atoms are here numbered for convenience along the chain consecutively from the NH_2; *thus* 5 *and* 6 *are the atoms of the central ethylene link. The unit of charge is* e/1000.

In the ground state the perturbation introduced by a single amino-group is hardly noticeable in the unsubstituted ring. Similar conclusions have been reached by Mme. A. Pullman (*Compt. rend.*, 1948, **226**, 486), who has published a charge and bond-order diagram for the ground state of aminostilbene, using the method of resonance among valence-bond structures. Her diagram agrees with our own as closely as the differences between the two methods would be expected to allow. The chief distinction between the two diagrams is in the scale of the charge migrations; Mme. Pullman's are about 2—3 times as large as ours. As we believe that our migrations are probably too large, hers should *a fortiori* be larger; but the relative values correspond well.

The last point which we wish to make refers to the alternating character of the charge migrations in the two aminostilbenes. It has been shown quite generally by Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1947, *A*, **192**, 16) that the effect of a substituent in the ground state of an aromatic or conjugated system is to increase or decrease the net charge on consecutive atoms in an alternating manner. This is particularly well illustrated in these aminostilbenes. Fig. 3 shows this alternating effect, and it also exhibits the decreasing influence of the substituent as we move away from the point of substitution. It appears that electronic excitation of the molecule to some extent destroys these alternations, though it increases the average charge migration. Quite apart from any other considerations, this would imply a greater reactivity than in the ground state. Thus the general picture of electronic excitation presented by Figs. 2 and 3 is that of an increased asymmetry of charge, resulting in reduced bonding and a greater proportion of the π electrons free to initiate reactions, particularly with electrophilic reagents.

We acknowledge the receipt of a grant from the Department of Scientific and Industrial Research which has enabled this work to be carried out.

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422. *Studies on the Nature of Chemisorptive Bonds. Part I. Some Observed Regularities.*

By E. B. Maxted.

Some observed regularities in connection with chemisorptive bonds on metallic hydrogenation catalysts have been summarised as a basis for the experimental work described in succeeding papers of the series. The capacity of an adsorbate to form a strong chemisorptive bond to a catalyst such as platinum appears to be determined by certain types of electronic structure, which are defined in the paper for three types of strongly held adsorbed species represented respectively by compounds containing catalytically toxic elements of the sulphur or the phosphorus group, by toxic metallic ions, and by strongly adsorbed molecules containing multiple bonds, such as carbon monoxide and ethylene. The conditions which are necessary for strong bonding form evidence for the importance of *d*-band structure in adsorption and in hydrogenation catalysis by transition metals. Thus, as has already been indicated by magnetic measurements (Dilke, Eley, and Maxted, *Nature*, 1948, **161**, 804) for methyl sulphide adsorbed on palladium, the adsorption of poisons of this type, with the consequent destruction of the catalytic activity, appears to involve electron transfer from the adsorbate into the *d*-band of the transition-metal catalyst, probably with the suppression of the fractional electron deficiencies in this band which, from a consideration of magnetic susceptibilities, seem to play a part in determining the catalytic activity. In the case of the poisoning of platinum catalysts with metallic ions, it is found that catalytic toxicity (which is an indication of strong adsorption) occurs only with metallic ions in which all five orbitals of a *d* shell, immediately preceding next-order *s* or *p* valency shells, are electronically occupied.

Regularities apparently also exist which correlate the catalytic activities of metals of the palladium and platinum groups with their paramagnetic susceptibilities.

Although the occurrence of some form of chemical bonding in chemisorptive linkages is inherent in the term chemisorption, little is known of the nature of such bonds. The subject is of special interest in connection with the mechanism of contact catalysis in which, in many cases, the components of the system catalysed—or some of these—become associated with a solid catalyst by the formation of chemisorptive bonds. The following two papers deal with adsorption on metallic hydrogenation catalysts; and, as an introduction to the experimental work described in these, it has been considered advisable to summarise some observed regularities which underlie and form the reason for these experimental studies.

In the first place it would seem that any investigation as to what structures are conducive to the production of the chemisorptive links formed in catalysis must include considerations of the structure both of the substances which are adsorbed and of the catalyst itself. This applies not only to hydrogenation but also to other types of contact catalysis in which, on grounds of specificity or strength of bonds and for other reasons, it appears that chemical bonding rather than general adsorption by van der Waals forces is involved. It appeared that a convenient first approach to the subject might be made by considerations derived from a study of catalyst poisoning, since the exhibition of toxic properties by a poison constitutes an easily recognisable indication of a strong bond.

It is known that strong bonds with metallic hydrogenation catalysts of the three transition groups represented by nickel, palladium, and platinum, with their neighbours, are formed by several general types of substance including, first, molecules containing sulphur, selenium, tellurium, phosphorus, arsenic, or antimony, secondly, a large number of metallic ions and, thirdly, substances, containing certain unsaturated bonds, such as carbon monoxide, cyanogen compounds, or ethylene, which is far more strongly adsorbed than, for instance, hydrogen.

Toxicity of Non-metals of Groups Vb and VIb.—In the case of catalyst poisons of the sulphur or the phosphorus class, it has been found (Maxted and Morrish, *J.*, 1940, 252) that toxicity is dependent on the presence, in the valency shell of the toxic element, of free electron pairs which are evidently necessary for the formation of the link with the catalyst, since the toxicity—*i.e.*, the power of forming a relatively strong chemisorptive bond—disappears if the structure of the molecule is such that the normally toxic element is associated with a completely shared electron octet. Thus, as has been shown in earlier papers, organic sulphides or thiols are toxic towards a platinum catalyst whereas sulphones or sulphonic acids are non-toxic :

Toxic	(R)C:S:C(R′)	(R)C:S:H
	Sulphide.	Thiol.
Non-toxic (shielded type)	(R)C:S:C(R′)	(R)C:S:OH
	Sulphone.	Sulphonic acid.

Indications have been obtained, by means of magnetic measurements (Dilke, Eley, and Maxted, *loc. cit.*), that electrons from, for instance, methyl sulphide probably enter the *d*-band of the adsorbing metal to give a co-ordinate link, the process being possibly accompanied by an elimination of any fractional electron deficiencies or holes in the *d*-band of the metal due to *d*–*s*-band overlap. It may be noticed that the sulphur atom should, after the electron transfer, be left with a formal positive charge the magnitude of which will depend on the extent of the transfer, an adsorption complex of the type $\overset{-}{M} \longleftarrow \overset{+}{S}(CH_3)_2$ being formed, in which the sign rather than the magnitude of the formal charges is indicated.

A further point of interest in connection with the above toxicity rule, namely, that strong bonds are not formed if free electron pairs in the valency shells of the sulphur atoms are absent, is to be found in the observation (Maxted and Walker, *J.*, 1948, 1093) that a nitrogen atom containing a free electron pair may be catalytically toxic. Thus, very carefully dried ammonia in, for instance, *cyclo*hexane solution was shown to be toxic towards a platinum catalyst, whereas the ammonium ion is non-toxic :

Toxic. Non-toxic.

This capacity of a nitrogen atom of a suitable electronic configuration (cf. sulphur) to form a strong adsorptive bond with a metallic hydrogenation catalyst is of interest in that it completes the toxic series, N, P, As, Sb, (Bi), in Group Vb.

Toxicity of Metallic Ions.—The poisoning of platinum or similar catalysts by toxic metal ions falls into a somewhat different category, since the adsorption complex probably resembles an intermetallic compound. Regularities have been brought out by a further analysis of earlier work (Maxted and Marsden, *J.*, 1940, 469) which was undertaken to determine which metallic ions are toxic towards platinum. It will be seen from Table I that toxicity—namely, the power of forming a strong adsorptive bond—appears to be confined to those metals in which all five orbitals of a *d* shell, immediately preceding *s* or *p* valency orbitals, are occupied by electron pairs or at least singly; and, since no toxicity is observed if unoccupied *d* orbitals of this nature are present, or if no *d* orbitals are possible, it seems probable that *d* electrons are in some way concerned in the intermetallic bond between the toxic metal and the catalyst. The toxic metals thus differ from the non-metallic elements of Groups Vb and VIb for which strong bonds to a transition metal catalyst can apparently be formed by *s* and *p* valency electrons. The term external orbitals in the heading to the table includes the valency orbitals and the *d* orbitals immediately preceding these.

All the metallic ions listed as toxic in Table I can, by partition measurements, be shown experimentally to be strongly and preferentially adsorbed on platinum or similar catalysts even when they are present in only vanishingly small concentrations, this capacity for strong bonding to the catalyst being, as with other poisons, the essential feature for toxicity. The evidence that these strongly adsorbed ions themselves act as the effective poisons, without a change for instance into a metallic deposit, lies largely in the observed reversibility of the adsorption, namely, in the existence of well-defined adsorption–desorption equilibria. This reversibility has been tested in water and in aqueous acetic acid solution for a number of toxic metallic ions, including copper, silver, zinc, cadmium, mercury, indium, thallium, tin, lead, manganese, iron, nickel, and cobalt (Maxted, *J.*, 1925, **127**, 73; Maxted and Evans, *J.*, 1938, 2071; Maxted and Marsden, *loc. cit.*, and subsequent work), the adsorption isotherms connecting the amount adsorbed on the catalyst with the residual concentration in the supernatant liquid being in every respect similar to those given by other poisons, *e.g.*, by alkyl sulphides.

Although any subsequent change in chemical form would not in any case affect the question of the primary toxic nature of the adsorbed ion, which follows from its observed strong adsorption, it may be desirable to recapitulate some of the further evidence that the toxic effect is not in general complicated, at any rate at room temperature, by the formation of metal deposits, which is the principal possible further reaction, particularly under hydrogenating conditions. This possibility of a hydrogenation or reduction product is analogous, for instance, to the behaviour of thiophen which, although primarily adsorbed as such, passes in the adsorbed state under hydrogenating conditions almost entirely into thiophan. If, in the case of poisoning with a metallic salt solution, the observed inhibitive effect were due to any extent to mechanical covering by a metal, the greatest toxicity would be expected from the most easily reducible

TABLE I.

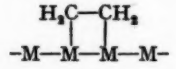
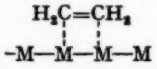
Metal ions tested.					Electronic occupation of external orbitals.	Toxicity towards platinum.
Li^+	Be^{2+}	Al^{3+}			No *d* shell	Non-toxic
Na^+	Mg^{2+}				No internal *d* shell	,,
K^+	Ca^{2+}				3*d* ○ ○ ○ ○ ○ | 4*s* ○	,,
Rb^+	Sr^{2+}		Zr^{4+}		4*d* ○ ○ ○ ○ ○ | 5*s* ○	,,
Cs^+	Ba^{2+}	La^{3+}			5*d* ○ ○ ○ ○ ○ | 6*s* ○	,,
		Ce^{3+}				
			Th^{4+}		6*d* ○ ○ ○ ○ ○ | 7*s* ○	,,
Cu^+	Zn^{2+}				3*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 4*s* ○	Toxic
Cu^{2+}					3*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 4*s* ○	,,
Ag^+	Cd^{2+}	In^{3+}			4*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 5*s* ○	,,
			Sn^{2+}		4*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 5*s* ⊙	,,
Au^+	Hg^{2+}				5*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 6*s* ○	,,
	Hg^+				5*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 6*s* ⊙	,,
		Tl^+	Pb^{2+}	Bi^{3+}	5*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 6*s* ⊙	,,
Cr^{2+}					3*d* ⊙ ⊙ ⊙ ⊙ ○ | 4*s* ○	Non-toxic
Cr^{3+}					3*d* ⊙ ⊙ ⊙ ○ ○ | 4*s* ○	,,
Mn^{2+}					3*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 4*s* ○	Toxic
Fe^{2+}					3*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 4*s* ○	,,
Co^{2+}					3*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 4*s* ○	,,
Ni^{2+}					3*d* ⊙ ⊙ ⊙ ⊙ ⊙ | 4*s* ○	,,

metals such as silver and gold, which is not the case. Further, any deposition of metal would not be expected in aqueous solution for many metallic ions which are toxic to platinum, including zinc, cadmium, indium, thallium, manganese, and possibly iron, cobalt, and nickel: moreover, as has been pointed out in previous papers, salts of catalytically poisonous metals have the same order of toxicity in acetic acid solution (in which still more of any possible metallic deposits would be soluble) as in water. It has also been found that the metallic salts which are poisonous for catalytic hydrogenation are also toxic in oxidation systems, for instance in the decomposition of hydrogen peroxide (Maxted, *J.*, 1922, **121**, 1760), their toxicity being again of the same order as for catalytic hydrogenation. Accordingly, the presence of hydrogenating conditions does not seem to be connected with the toxic character of these ions at room temperature.

It is of course well known from the work of Ipatiew and his co-workers (*Ber.*, 1927, **60**, 1982; 1928, **61**, 624, and other papers) that, at high temperatures and at high hydrogen pressures, aqueous solutions of many metallic salts can be reduced to the metal: thus, at a hydrogen pressure of 80 atm., the reduction of lead nitrate or acetate solution to lead is stated to begin at 275°; but, from the evidence given above, reduction to metal does not appear to occur at room temperature and pressure.

Strongly Adsorbed Substances containing Unsaturated Bonds.—A third condition for strong adsorption by a transition-group metal seems to be the possession of an unsaturated bond. This class of adsorbate is of considerable importance since it includes normal reactants—namely, the type of substance which is most usually subjected to catalytic hydrogenation—rather than extraneous catalyst poisons. By virtue, however, of rather wide differences in the strength of the adsorption bond for different individual members of the class, more strongly held unsaturated substances are also capable of acting as inhibitants towards the adsorption of less strongly held species. Thus carbon monoxide acts as a strong catalyst poison in the hydrogenation of ethylenic substances, benzene even in small concentrations retards the hydrogenation of *cyclo*hexene, and ethylene suppresses the chemisorption of hydrogen, with its attendant dissociation into atoms, at nickel or platinum surfaces: indeed, Twigg and Rideal (*Proc. Roy. Soc.*, 1939, *A*, **171**, 55) have shown that, in the hydrogenation of ethylene on nickel, no chemisorbed hydrogen atoms are present, and that the mechanism of the hydrogenation process involves the interaction of chemisorbed ethylene with hydrogen molecules which are less strongly adsorbed and may be held merely by van der Waals forces.

In the adsorption of a molecule containing an unsaturated bond a new condition arises, in that, in place of the formation of some type of normal covalent bond by interaction with the electron system of the metal, the adsorption may take place by the participation of the metal in a resonance system of the bond-multiplicity type. This type of bond seems particularly probable for adsorbates which are already in a strongly resonating state, *e.g.*, for carbon monoxide; but it is also possible for ethylene, in which bond-multiplicity resonance is low or absent in an unadsorbed state, the resonance complex for ethylene adsorbed on a metal, M, corresponding with a bond hybridisation of components of the type (I) and (II), in which either

(I.)  (II.) 

of these structures may predominate. From an analogy to the dative bonds with sulphur and from the general importance which the structure of the *d* band of transition metals appears to possess in catalysis, it might be expected that this fractional bonding would be to the *d* band of the metal, in which fractional electronic deficiencies occur which seem to be the seat of the catalytic activity and, since adsorption is a necessary factor in the catalysis, also of the adsorptive bonding.

Correlation between Catalytic Activity and Magnetic Properties.—In the above sections the formation of a strong chemisorptive bond towards a metallic hydrogenation catalyst has been considered mainly from the standpoint of various types of strongly held adsorbates. Any approach to the probable nature of such bonds must however also include a consideration of what configurations in the adsorbing metals themselves appear to be conducive to bond formation.

If the three groups of transition elements employed for catalytic hydrogenation are set out in order of ascending atomic number, as in Table II, it will be seen that those metals which are

TABLE II.

Fe (26)	Co (27)	Ni (28)	Cu (29)
Ru (44)	Rh (45)	Pd (46)	Ag (47)
Os (76)	Ir (77)	Pt (78)	Au (79)

ordinarily associated with the most effective catalytic properties for hydrogenation fall under one another and that the activities observed in practice appear to vary, in each horizontal series, in such a way that the activity rises horizontally to a maximum at the elements enclosed in the frame and subsequently falls steeply, in that copper, silver, and gold—all of which have a completely occupied *d* shell—possess a low or even zero activity for catalytic hydrogenation.

It is of interest to note that this activity sequence is followed by the value of the paramagnetic susceptibility—at least in the two platinum-metal series, in which measurements of this susceptibility are less complicated by ferromagnetism than in the iron group and can be carried out directly in the temperature range in which platinum-metal catalysts are usually employed—this susceptibility being determined by the structure of the *d*-band, including fractional *d*-electron deficiencies or positive holes due to *d*–*s*-band overlap (which vanish in the fully occupied vertical series, copper, silver, gold) and by terms due to correlation forces (see Mott and Jones, "Theory of the Properties of Metals and Alloys," Oxford, 1936, pp. 141, 196). Values for the magnetic susceptibilities, χ, in 10^{-6} c.g.s. electromagnetic units per g. and per g.-atom at 18°, are given for the two platinum-metal groups in Table III, from which a rise to a maximum at palladium and platinum, respectively, and a subsequent fall to less than zero for silver and gold will be seen, both of these metals being diamagnetic.

This apparent connection between activity and paramagnetic susceptibility, at any rate for the groups dealt with in Table III, seems to indicate that the catalytic activity is determined by the structure of the *d* band; and, above all, the disappearance of catalytic properties with the disappearance of fractional electron deficiencies in this band strongly suggests that these deficiencies play a critical part in hydrogenation catalysis and in adsorption connected with

TABLE III.

Metal	Ru	Rh	Pd	Ag
χ_g.	+ 0·50	+ 1·11	+ 5·4	− 0·20
$\chi_{g\text{-at.}}$	+50·8	+114·2	+476·2	−21·6
Metal	**Os**	**Ir**	**Pt**	**Au**
χ_g.	+ 0·05	+ 0·14	+ 1·10	− 0·15
$\chi_{g\text{-at.}}$	+ 9·5	+ 29·0	+214·7	−29·6

this. A similar inference can be obtained by considering the probable mechanism of inactivation by poisoning, in that it has been shown that the suppression of the catalytic activity of a typical transition element by the adsorption of methyl sulphide involves electron transfer into the *d* band of the metal; and it accordingly seems by no means improbable that the poisoning process may consist of, or include essentially, the elimination of the *d*-band deficiency.

UNIVERSITY OF BRISTOL. [*Received, March 16th,* 1949.]

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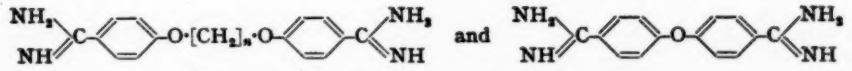
423. *Nuclear-substituted Derivatives of 4 : 4′-Diaminodiphenyl Sulphone.*

By S. S. BERG.

4 : 4′-Diaminodiphenyl sulphone has been substituted in the *ortho*-positions to the sulphone bridge with halogen and hydroxyl groups.

INTRODUCTION of nuclear halogen and hydroxyl groups into symmetrical diamidines of the types

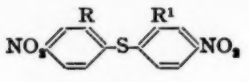


has been shown to yield products of enhanced bactericidal activity (Berg and Newbery, this vol., p. 642). The therapeutic effect of 4 : 4-diaminodiphenyl sulphone on infections caused by bacilli pathogenic to man prompted an investigation into the effects of similar substituents in the *ortho*-position to the sulphone linkage.

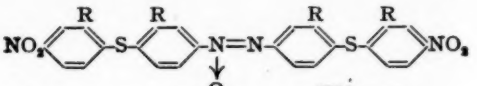
On account of their extreme insolubility, and ease of hydrolysis of their salts in aqueous solution, the halogen derivatives were tested orally *in vivo* against *Staph. aureus* and *Strep. pyogenes* in mice. A decrease in toxicity in the order Cl < Br < I, together with corresponding decrease in activity, was observed. These results were almost certainly due to the poor absorption of the products. Whilst this work was in progress Youmans and Doub (*Amer. Rev. Tuberc.*, 1946, **54**, 287) and Youmans, Feldman, and Doub (*ibid.*, p. 295) reported that 2-chloro- and 2-hydroxy-4 : 4′-diaminodiphenyl sulphone were less active than 4 : 4′-diaminodiphenyl sulphone for the virulent *Mycobacterium tuberculosis*, human type, *in vitro*, and that the 2-chloro-derivative was inactive *in vivo*. In view of these results further work in this series was not undertaken, but the chemical work is now published because of the appearance of a paper by Hodgson, Dodgson, and Smith (*J.*, 1948, 1104) in which two of the intermediates prepared during the course of this work are described. Although 2-chloro- and 2-hydroxy-4 : 4′-diaminodiphenyl sulphone are listed by Wiselogle in his "Survey of Antimalarials," the preparation and properties of the former had not been described, but the latter compound, now prepared by an unambiguous route, was identical with that described by Burton and Hoggarth (*J.*, 1945, 469), so its structure is now established.

The mono- and di-substituted halogen derivatives were obtained by the oxidation of 2- and 2 : 2′-halogenated 4 : 4′-dinitrodiphenyl sulphide (I), followed by reduction of the nitro-groups. Oxidation was effected with potassium permanganate; use of hydrogen peroxide gave products contaminated with the corresponding sulphoxide. The condensation of sodium *p*-nitrothiophenoxide with the appropriate 1-chloro-2-halogeno-4-nitrobenzene gave (I; R′ = H). When R = R′ = Cl or I, condensation of the appropriate 1-chloro-2-halogeno-4-nitrobenzene with sodium sulphide gave the required sulphide in poor yield. The latter reaction gave also an

appreciable amount of a highly coloured, non-basic compound probably, (II), obtained by reduction of (I).



(I.)



(II.)

4 : 4′-*Diamino*-2-*hydroxydiphenyl sulphone* was obtained by the reduction of 4 : 4′-*dinitro*-2-*hydroxydiphenyl sulphone*, prepared as its *acetate* by the oxidation of 4 : 4′-*dinitro*-2-*acetoxydiphenyl sulphide*. Condensation of *p*-nitrobenzenethiol with 2-*bromo*-5-*nitrophenyl acetate* in acetone–potassium carbonate yielded the required sulphide.

Experimental.

1-*Chloro*-2-*bromo*-4-*nitrobenzene*.—A suspension of 2-bromo-4-nitroaniline (Rowe, Jambuserwal, and Partridge, *J.*, 1935, 1135) (18·5 g.) in hydrochloric acid (*d* 1·16; 75 c.c.) was added to ice (100 g.) and sodium nitrite (7·5 g.). The solution was added dropwise (during 30 minutes) to cuprous chloride (12·5 g.) in hydrochloric acid (*d* 1·16; 50 c.c.) at 20—25°. Nitrogen was evolved, and after an hour's heating at 90°, an oil separated which solidified on cooling. The solid was collected, washed successively with water, dilute sodium hydroxide, and water, and then dried. The *product* (12·5 g.) distilled as a yellow oil, b. p. 100°/0·1 mm., which crystallised in white fluffy needles, m. p. 61°, from light petroleum (b. p. 40—60°) (Found : C, 30·5; H, 1·4; N, 5·9. $C_6H_3O_2NClBr$ requires C, 30·4; H, 1·3; N, 6·0%).

2-*Chloro*-4 : 4′-*dinitrodiphenyl Sulphide*.—*p*-Nitrobenzenethiol (Mayer, *Ber.*, 1909, **42**, 3050) (1·55 g.) and sodium hydroxide (0·4 g.) in ethanol (20 c.c.) were added to a boiling solution of 3 : 4-dichloronitrobenzene (1·9 g.) in ethanol (10 c.c.). A solid was precipitated after 10 minutes, and after being heated under reflux for 2 hours the mixture was cooled, and the solid collected. The *sulphide* (1·3 g.) crystallised from acetic acid in yellow prisms, m. p. 144° (Found : N, 9·0; Cl, 11·6. $C_{12}H_7O_4N_2ClS$ requires N, 9·0; Cl, 11·5%).

2-*Bromo*-4 : 4′-*dinitrodiphenyl sulphide*, yellow prismatic needles (from acetic acid), m. p. 159° (Found : N, 8·0; Br, 22·6. $C_{12}H_7O_4N_2BrS$ requires N, 7·9; Br, 22·5%), and 2-*iodo*-4 : 4′-*dinitrodiphenyl sulphide*, yellow prisms (from acetic acid), m. p. 168° (Found : N, 6·9; I, 31·1; S, 8·0. $C_{12}H_7O_4N_2IS$ requires N, 7·0; I, 31·6; S, 8·0%), were prepared similarly from 1-chloro-2-bromo- and 2-iodo-4-nitrobenzene (Willgerodt and Arnold, *Ber.*, 1901, **34**, 3344), respectively.

2 : 2′-*Dichloro*-4 : 4′-*dinitrodiphenyl Sulphide*.—A stirred, boiling solution of 3 : 4-dichloronitrobenzene (15 g.) in ethanol (60 c.c.) was treated, during 5 minutes, with sodium sulphide nonahydrate (10 g.) in 25% aqueous ethanol (40 c.c.). After being heated under reflux for 6 hours, the mixture was cooled, and the solid collected and washed with hot water, dilute hydrochloric acid, ethanol, and ether. The solid was then extracted with boiling 95% acetic acid; the sulphide (7·2 g.) separated in yellow prisms, m. p. 163° (Found : N, 8·2; Cl, 21·0; S, 9·4. Calc. for $C_{12}H_6O_4N_2Cl_2S$: N, 8·2; Cl, 20·7; S, 9·3%). Hodgson *et al.* (*loc. cit.*) describe the product as crystallising in yellow needles, m. p. 166°.

The solid (3 g.) which was insoluble in 95% acetic acid crystallised from benzene, and then from acetic acid, in large red prisms, m. p. 195° (Found : C, 45·0; H, 2·2; N, 8·5; Cl, 22·0; S, 10·25. $C_{24}H_{12}O_5N_4Cl_4S_2$ requires C, 45·0; H, 1·9; N, 8·7; Cl, 22·1; S, 10·0%).

2 : 2′-*Di-iodo*-4 : 4′-*dinitrodiphenyl sulphide*, pale red rhombs (from 90% aqueous acetic acid), m. p. 186° (Found : N, 5·2; I, 47·8. $C_{12}H_6O_4N_2I_2S$ requires N, 5·3; I, 48·1%), was prepared similarly.

2-*Bromo*-5-*nitrophenyl Acetate*.—Treatment of 2-bromo-4-nitrophenol (Henley and Turner, *J.*, 1930, 938) with acetic anhydride gave the *acetate*, which formed pale yellow needles, m. p. 86°, from ethanol (Found : N, 5·3; Br, 30·6. $C_8H_6O_4NBr$ requires N, 5·4; Br, 30·8%).

4 : 4′-*Dinitro*-2-*acetoxydiphenyl Sulphide*.—2-Bromo-5-nitrophenyl acetate (13 g.), *p*-nitrobenzenethiol (7·8 g.), fused potassium carbonate (3·5 g.), and acetone (100 c.c.) were heated under reflux for 2 hours. After filtration, the filtrate yielded the *sulphide* (6·0 g.), which crystallised in yellow prisms, m. p. 100°, from ethanol (Found : C, 50·1; H, 3·1; N, 8·2. $C_{14}H_{10}O_6N_2S$ requires C, 50·3; H, 3·0; N, 8·4%).

2-*Chloro*-4 : 4′-*dinitrodiphenyl Sulphone*.—Potassium permanganate (7·5 g.) in hot water (50 c.c.) was added dropwise, with stirring, to 2-chloro-4 : 4′-dinitrodiphenyl sulphide (10 g.) in boiling acetic acid (150 c.c.). After addition was complete, water (150 c.c.) was added, and the cooled mixture decolorised with sulphur dioxide. The *sulphone* (8·0 g.) was collected, and crystallised from 70% aqueous acetic acid in long white needles, m. p. 182—183° (Found : N, 8·2; Cl, 10·6. $C_{12}H_7O_6N_2ClS$ requires N, 8·2; Cl, 10·4%).

The following were obtained similarly : 2-*bromo*-4 : 4′-*dinitrodiphenyl sulphone*, white needles, m. p. 162°, from 70% aqueous acetic acid (Found : N, 7·0; Br, 20·8. $C_{12}H_7O_6N_2BrS$ requires N, 7·2; Br, 20·7%); 2-*iodo*-4 : 4′-*dinitrodiphenyl sulphone*, pale yellow needles, m. p. 165°, from 70% aqueous acetic acid (Found : N, 6·4; I, 29·0; S, 7·6. $C_{12}H_7O_6N_2IS$ requires N, 6·4; I, 29·3; S, 7·4%); 2 : 2′-dichloro-4 : 4′-dinitrodiphenyl sulphone, orange plates, m. p. 218°, from acetic acid (Found : N, 7·5; Cl, 18·7; S, 8·6. Calc. for $C_{12}H_6O_6N_2Cl_2S$: N, 7·5; Cl, 18·8; S, 8·5%) (Hodgson *et al.*, *loc. cit.*, describe the same compound as crystallising in colourless needles, m. p. 169°); and 2 : 2′-*di-iodo*-4 : 4′-*dinitrodiphenyl sulphone*, yellow prisms, m. p. 260°, from acetic acid (Found : N, 5·2; I, 45·1. $C_{12}H_6O_6N_2I_2S$ requires N, 5·0; I, 45·4%).

4 : 4′-*Dinitro*-2-*hydroxydiphenyl Sulphone*.—4 : 4′-Dinitro-2-acetoxydiphenyl sulphide was oxidised with potassium permanganate in boiling aqueous acetic acid, and the solid, collected after decolorisation with sulphur dioxide, was readily hydrolysed with boiling aqueous sodium carbonate. The *sulphone*

separated in yellow prismatic needles, m. p. 216°, from acetic acid (Found: C, 44·2; H, 2·4; N, 8·6. $C_{12}H_8O_7N_2S$ requires C, 44·2; H, 2·5; N, 8·6%).

2-Chloro-4 : 4'-diaminodiphenyl Sulphone.—Reduced iron (10 g.) was added slowly to a boiling solution of 2-chloro-4 : 4'-dinitrodiphenyl sulphone (5 g.) in 60% aqueous acetic acid (200 c.c.). After being heated at 90° for 10 minutes, the mixture was filtered, and the filtrate diluted with water (600 c.c.). The solid was collected, washed with water, and dissolved in warm 2N-hydrochloric acid (50 c.c.). The solution was basified with 2N-sodium hydroxide, and the *sulphone* (3·0 g.) collected. It separated in pale yellow prismatic needles, m. p. 114°, from dilute acetic acid (Found: N, 9·9; Cl, 12·7. $C_{12}H_{11}O_2N_2ClS$ requires N, 9·9; Cl, 12·6%). The following were prepared similarly: *2-bromo-4 : 4'-diaminodiphenyl sulphone*, yellow needles, m. p. 157°, from dilute acetic acid (Found: N, 8·7; Br, 24·5; S, 10·1. $C_{12}H_{11}O_2N_2BrS$ requires N, 8·6; Br, 24·4; S, 9·8%); *2-iodo-4 : 4'-diaminodiphenyl sulphone*, buff needles, m. p. 207°, from aqueous acetic acid (Found: N, 7·4; I, 33·5. $C_{12}H_{11}O_2N_2IS$ requires N, 7·5; I, 34·0%); *2 : 2'-dichloro-4 : 4'-diaminodiphenyl sulphone*, orange needles, m. p. 263°, from aqueous acetic acid (Found: N, 9·0; Cl, 22·6; S, 10·1. $C_{12}H_{10}O_2N_2Cl_2S$ requires N, 8·9; Cl, 22·4; S, 10·0%); and *2 : 2'-di-iodo-4 : 4'-diaminodiphenyl sulphone*, white prismatic needles, m. p. 280°, from aqueous acetic acid (Found: N, 5·7; I, 50·6. $C_{12}H_{10}O_2N_2I_2S$ requires N, 5·6; I, 50·8%).

4 : 4'-Diamino-2-hydroxydiphenyl Sulphone.—4 : 4'-Dinitro-2-hydroxydiphenyl sulphone (10 g.) in boiling 90% aqueous acetic acid (150 c.c.) was treated with iron powder (10 g.). The mixture was filtered, and the filtrate evaporated to dryness. Treatment with 3N-sulphuric acid yielded the *sulphate* (10 g.) of the diamino-sulphone, which crystallised in white prismatic needles, m. p. 208° (decomp.), from 2N-sulphuric acid (Found: C, 31·4; H, 3·3; N, 6·2. $C_{12}H_{12}O_2N_2S,2H_2SO_4$ requires C, 31·3; H, 3·5; N, 6·1%). Neutralisation of the hot aqueous solution of the sulphate with sodium acetate yielded the base as white needles, m. p. 134—135°, from water. This was identical with the compound described by Burton and Hoggarth (*loc. cit.*).

Thanks are due to Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanalyses, to Dr. J. N. Ashley for his interest, and to the Directors of Messrs. May and Baker Ltd. for permission to publish the results.

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424. *Butylnaphthalenes and their Derivatives. Part II. Derivatives of* 2-tert.-*Butylnaphthalene, and the Orientation of Two Di-*tert.-*butylnaphthalenes.*

By R. B. CONTRACTOR, A. T. PETERS, and (the late) F. M. ROWE.

Nitro-, amino-, sulpho-, and *hydroxy*-derivatives of 2-*tert.*-butylnaphthalene have been prepared, and the orientation of two di-*tert.*-butylnaphthalenes, m. p. 145—146°, and 85—90°, is examined.

THE preparation of 2-*tert.*-butylnaphthalene (I) and the determination of its orientation by oxidation and synthesis are recorded by Bromby, Peters, and Rowe (*J.*, 1943, 144). Its nitration and subsequent reduction, and sulphonation, are now described. Thus, with diacetylorthonitric acid (Pictet and Genequand, *Ber.*, 1902, **35**, 2526) at 0—5°, (I) afforded 1-*nitro*-2-tert.-*butylnaphthalene*, reduced by boiling aqueous-alcoholic sodium hydrosulphite (dithionite) to the corresponding *amine* (II); in ether solution the oily base gave a crystalline hydrochloride and a sulphate, it was diazotised by nitrosylsulphuric acid and converted into 1-(2-tert.-*butylnaphthalene*-1-*azo*)-2-*hydroxy*-3-*naphthoic anilide*, and with *p*-nitrobenzenediazonium chloride, it acted as coupling component to yield impure 1-amino-4-*p*-nitrobenzeneazo-2-*tert.*-butylnaphthalene.

Sulphonation of (I) with concentrated sulphuric acid at 95—100° gave 6-*tert.*-butylnaphthalene 2-sulphonic acid, isolated through the *barium* salt, and characterised as the *sulphonamide* and S-*benzylthiuronium* derivative. It was converted by alkaline fusion at 260—280° into 6-tert.-*butyl*-2-*naphthol* (III). A similar sulphonation of 2-ethylnaphthalene gave the 6-sulpho-derivative (Levy, *Compt. rend.*, 1936, **202**, 1679).

An isomeric *tert.*-butylnaphthol was formed by *tert.*-butylation of 2-naphthol. Thus, Diels and Stein (U.S.P. 1,788,529) and Tschitschibabin (*Bull. Soc. chim.*, 1935, **2**, 1497; *Bull. Acad. Sci. U.S.S.R.*, 1935, 951) record the preparation of a *tert.*-butyl-2-naphthol (the former authors giving m. p. 102° and the latter m. p. 113°) using aluminium chloride and phosphoric acid, respectively, as condensing agent; no orientation is given by Tschitschibabin, but the former authors suggest that the product is 4-*tert.*-butyl-2-naphthol. National Aniline Co. (U.S.P. 2,090,938) describe the interaction of 2-naphthol, *iso*butyl chloride, and zinc chloride, to give a mixture containing a *tert.*-butyl-2-naphthol, which was used without further purification as an intermediate for plastics and azo-dyes. The present authors have treated 2-naphthol with

tert.-butyl chloride in the presence of zinc chloride, aluminium chloride, and phosphoric acid, whereupon the same *tert.*-butyl-2-naphthol (IV), m. p. 119—120° (*picrate*, m. p. 142°), is formed. The sparingly soluble sodium salt of (IV) separates in colourless flakes from a 5% aqueous sodium hydroxide extract of the reaction mixture; this is a much improved method of purification. The alkali-insoluble residue, which is always formed, is the tert.-*butyl ether*, m. p. 139°, of (IV), also obtained from (IV) and *tert.*-butyl chloride in the presence of zinc chloride. The varying m. p.s of (IV) recorded by previous workers are probably due to incomplete separation by the fractional-distillation method used. Compound (IV) readily formed an *acetate*, and as a coupling component it was converted into m- and p-*nitrobenzeneazo*-derivatives, reduced by aqueous-alcoholic sodium hydrosulphite (dithionite) to a 1-*amino*-2-*hydroxy*-tert.-*butylnaphthalene*, which was decomposed on attempted oxidation. However, the ready formation of the above azo-derivatives excludes substitution of the *tert.*-butyl group in the 1-position, and the *tert.*-butyl group in (IV) probably occupies the 4-position, *i.e.*, in the same ring as the hydroxy-group.

Although di-*tert.*-butylnaphthalenes have been described in the literature, their orientations have not been determined. Gump (*J. Amer. Chem. Soc.*, 1931, **53**, 380) isolated two di-*tert.*-butylnaphthalenes, m. p. 82—83° and 145—146°, which Wegscheider (*Monatsh.*, 1884, **5**, 236) had suggested were 1 : 1- and 1 : 2-dinaphthyls. Fieser and Price (*J. Amer. Chem. Soc.*, 1936, **58**, 1841) recorded m. p. 86—90° for the isomer of lower m. p., whilst Tsukervanik and Terentieva (*J. Gen. Chem. Russia*, 1937, **7**, 637) stated that *tert.*-butyl alcohol, naphthalene, and aluminium chloride gave a di-*tert.*-butylnaphthalene, m. p. 132° (picrate, m. p. 99°), and Calcott (*J. Amer. Chem. Soc.*, 1939, **61**, 1010), using hydrofluoric acid as condensing agent, obtained a derivative of m. p. 143°. Price and collaborators (*J. Org. Chem.*, 1942, **7**, 517) recorded m. p.s of 80—82° and 145—146° for the two di-*tert.*-butylnaphthalenes, and stated that repeated crystallisation of the former raised its m. p. to 103—104°. The present authors have worked for several years on these derivatives, and substantiate the experimental work of Price *et al.* Di-*tert.*-butylnaphthalene, m. p. 145—146°, does not form a picrate and can be readily separated from the more soluble isomer; the latter, when regenerated from its picrate, has m. p. 85—90°, and in this regenerated product the possibility of the presence of a closely-related isomer (*e.g.*, 2 : 6 and 2 : 7) is not overlooked.

The determination of the orientation of the two isomers has now been attempted; previous attempts by Price *et al.* (*loc. cit.*) by nitric acid oxidation failed. The well-known stability of the *tert.*-butyl group to oxidising agents (cf. Bromby *et al.*, *loc. cit.*, naphthalene series; Peters, *J.*, 1942, 562, acenaphthene series) is a vital factor in oxidation experiments. One of the *tert.*-butyl groups in both di-*tert.*-butylnaphthalenes must be in the β-position, as the same mixture results by *tert.*-butylating naphthalene and 2-*tert.*-butylnaphthalene.

Chromic acid oxidation of the di-*tert.*-butylnaphthalene, m. p. 145—146°, afforded a steam-volatile di-*tert.*-butyl-1 : 4-naphthaquinone, m. p. 83°, which (*a*) gave a *phenylhydrazone*, probably possessing the *p*-hydroxyazo-structure (cf. Linke *et al.*, *Ber.*, 1884, **17**, 3026), (*b*) was convertible into 1 : 4-diacetoxydi-*tert.*-butylnaphthalene (V), m. p. 132—133°, and (*c*) was oxidised by boiling aqueous permanganate, followed by alkaline hydrogen peroxide, to an acid agreeing in analysis with the data required for a di-*tert.*-butylphthalic acid. This suggests that both *tert.*-butyl groups are in the same ring in the di-*tert.*-butylnaphthalene, m. p. 145—146°, which is possibly the 1 : 3-derivative.

The di-*tert.*-butylnaphthalene, m. p. 85—90°, gave a difficultly steam-volatile quinone, which (*a*) afforded a *phenylhydrazone*, differing from that obtained similarly from the other isomer, (*b*) was converted by reductive acetylation into a diacetoxy-derivative, m. p. 114—120°, which on repeated crystallisation gave colourless needles, m. p. 132—133°, not depressed on admixture with (V) (this anomalous behaviour is not clear), and (*c*) was oxidised by permanganate to give a low yield of an acid, the analysis of which suggested a mono-*tert.*-butylphthalonic acid. Thus, the *tert.*-butyl groups are probably in different rings in the di-*tert.*-butylnaphthalene, m. p. 85—90°, which is probably the 2 : 6-derivative. However, as this was possibly a mixture of isomers, the results are not regarded as conclusive. We regard the isomer, m. p. 85—90°, as a compound in which the *tert.*-butyl groups are certainly in different rings.

Experimental.

Preparation of 2-tert.-*Butylnaphthalene and the Two Di*-tert.-*butylnaphthalenes* (cf. Bromby *et al.*, *loc. cit.*).—The method of isolation of the mixed *tert.*-butylnaphthalenes was modified. The reaction mixture was cooled in an ice–salt mixture, filtered, and the filtrate distilled with steam until the last traces of naphthalene were removed; the dried oil was then fractionally distilled to give 2-*tert.*-butylnaphthalene, b. p. 128°/6 mm., and almost equal amounts of two di-*tert.*-butylnaphthalenes, m. p.

145—146°, and m. p. 85—90°. The latter formed a picrate, orange needles, m. p. 157—158°, decomposed by 5% aqueous sodium hydroxide to the hydrocarbon, m. p. 85—90°; repeated crystallisation of the latter from alcohol gave a product, m. p. 102—103°. The same mixture of di-*tert.*-butylnaphthalenes resulted from the *tert.*-butylation of authentic 2-*tert.*-butylnaphthalene.

1-*Nitro*-2-tert.-*butylnaphthalene*.—Diacetylorthonitric acid (38 g., 33 c.c., 1·25 mols.) was added to a well-stirred mixture of 2-*tert.*-butylnaphthalene (30 g.; 1 mol.) and acetic anhydride (30 c.c.) at 0—5° during one hour. After being left overnight at room temperature, the mixture was added to ice and extracted with ether and the ether extract was washed well with aqueous sodium carbonate and water until free from acid, and dried (Na_2SO_4). After removal of the ether, the residue was distilled, giving the *nitro*-compound as a colourless oil, b. p. 250°/85 mm. (22·8 g.; 60%), which on being kept became reddish-brown (Found: C, 74·0; H, 6·6; N, 6·5. $C_{14}H_{15}O_2N$ requires C, 73·3; H, 6·55; N, 6·1%). Numerous attempts at further nitration gave only a resinous polynitro-derivative, and no crystalline derivative of definite m. p. could be characterised.

1-*Amino*-2-tert.-*butylnaphthalene* (II).—The above mononitro-compound (40 g.) was suspended in alcohol (300 c.c.) and the mixture refluxed gently during the addition (2 hours) of sodium hydrosulphite (dithionite) (160 g.) in water (350 c.c.). The mixture was diluted with water and extracted with ether yielding an oil, which when distilled gave the *amine* (II) as a reddish-brown oil, b. p. 238—242°/85 mm. (13·5 g.; 41%) (Found: C, 84·0; H, 9·0; N, 7·0. $C_{14}H_{17}N$ requires C, 84·4; H, 8·5; N, 7·0%). Attempted preparation of the acetyl and toluene-*p*-sulphonyl derivatives gave sticky solids. The hydrochloride and sulphate, which were sticky when obtained from aqueous solution, were obtained in colourless crystals when a solution of the base in dry ether was treated with dry hydrogen chloride and monohydrate, respectively. Attempted oxidation of the amine with chromic acid gave only resins.

1-(2-tert.-*Butylnaphthalene*-1-*azo*)-2-*hydroxy*-3-*naphthanilide*.—A solution of the amine (II) (3 g.) in acetic acid (30 c.c.) was added to nitrosylsulphuric acid at 5° and the mixture poured on ice and filtered; the clear filtrate was coupled with Naphthol AS to give the *azo*-derivative (4 g.), which crystallised from acetic acid in lustrous greenish-violet prisms, decomp. 145—150° (Found: C, 77·8; H, 5·4; N, 8·5. $C_{31}H_{27}O_2N_3$ requires C, 78·6; H, 5·7; N, 8·9%), which gave a blue solution in cold concentrated sulphuric acid.

1-*Amino*-4-p-*nitrobenzeneazo*-2-tert.-*butylnaphthalene*.—Diazotised *p*-nitroaniline (1·5 g.) was added to a solution of the amine (II) (1·5 g.) in alcohol (100 c.c.) at room temperature. After 15 minutes, sodium acetate was added and the residue of *azo*-dye separated from aqueous acetic acid as an amorphous powder, m. p. 146—150° (Found: N, 18·2. $C_{20}H_{20}O_2N_4$ requires N, 16·4%).

6-tert.-*Butylnaphthalene*-2-*sulphonic Acid*.—2-*tert.*-Butylnaphthalene (54 g.) and concentrated sulphuric acid (45 g.) were heated at 95—100° for 7 hours, the mixture was then kept overnight at room temperature and poured into ice-water. Unchanged 2-*tert.*-butylnaphthalene was removed by extraction with ether, and the aqueous solution treated with barium carbonate and the *barium* salt of the sulphonic acid isolated (Found: C, 48·6; H, 4·9; S, 8·9. $C_{28}H_{30}O_6S_2Ba,2H_2O$ requires C, 48·05; H, 4·9; S, 9·15%). Potassium sulphate converted this into the *potassium* salt (Found: S, 10·7. $C_{14}H_{13}O_3SK$ requires S, 10·6%), which with excess of phosphorus pentachloride afforded the acid chloride as a sticky mass (solidifies at −15°), and thence the *sulphonamide*, colourless prisms (from aqueous alcohol), m. p. 201—202° (Found: C, 63·9; H, 6·3; N, 5·5; S, 12·7. $C_{14}H_{17}O_2NS$ requires C, 63·9; H, 6·5; N, 5·3; S, 12·2%). The S-*benzylthiuronium* derivative crystallised from alcohol in colourless prisms, m. p. 210—211° (Found: C, 61·6; H, 6·2; N, 5·9; S, 15·3. $C_{22}H_{26}O_3N_2S_2$ requires C, 61·4; H, 6·05; N, 6·0; S, 15·0%).

6-tert.-*Butyl*-2-*naphthol* (III).—The powdered potassium salt (20 g.) above was added to a stirred melt of sodium hydroxide (50 g.) and water (3 c.c.) at 230°. After the temperature had been slowly raised to 260° (30 minutes) and then to 280°, the melt was kept at this temperature for 40 minutes. The resulting oily layer was separated and extracted with dilute sodium hydroxide solution. The alkaline extract was acidified and extracted with ether, the ether extract dried (Na_2SO_4), and the residue distilled to give the *naphthol* as a pale yellow oil, b. p. 239—241°/160 mm. (Found: C, 83·3; H, 7·5. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%).

4(?)-tert.-*Butyl*-2-*naphthol* (IV).—(*a*) 2-Naphthol (50 g.), light petroleum (b. p. 60—80°) (150 c.c.), and anhydrous zinc chloride (15 g.) were stirred at room temperature during the addition of *tert.*-butyl chloride (50 g.). The mixture was gradually heated to 70° (oil-bath) and kept at this temperature for one hour, and then at 70—95° for 4 hours. After removal of excess of *tert.*-butyl chloride and light petroleum, the residue was boiled with 5% aqueous sodium hydroxide (1200 c.c.) and filtered; on cooling, the filtrate deposited colourless flakes of the sodium salt of a *tert.*-butyl-2-naphthol, converted by hydrochloric acid into 4(?)-*tert.*-butyl-2-naphthol (IV) (21 g.), which crystallised from light petroleum in colourless plates, m. p. 119—120° (Found: C, 83·9; H, 7·9. Calc. for $C_{14}H_{16}O$: C, 84·0; H, 8·0%). The residue (30 g.) insoluble in sodium hydroxide was crystallised from light petroleum, and 2-tert.-*butoxy*-4(?)-tert.-*butylnaphthalene* separated in colourless needles, m. p. 138—139° (Found: C, 84·3; H, 9·5. $C_{18}H_{24}O$ requires C, 84·3; H, 9·4%). The ether could be prepared directly from the naphthol (IV) by further *tert.*-butylation in presence of zinc chloride.

The *picrate* of (IV) crystallised from alcohol in orange needles, m. p. 142° (Found: C, 55·9; H, 4·2; N, 9·8. $C_{20}H_{19}O_8N_3$ requires C, 55·9; H, 4·4; N, 9·8%). The *acetate* of (IV) separated from alcohol in colourless needles, m. p. 64° (Found: C, 79·8; H, 7·8. $C_{16}H_{18}O$ requires C, 79·3; H, 7·4%). Coupling of *m*-nitrobenzenediazonium chloride to (IV) in aqueous-alcoholic sodium hydroxide gave the m-*nitrobenzeneazo*-derivative, which crystallised from acetic acid in orange-red needles, m. p. 177° (Found: C, 69·6; H, 5·2; N, 11·7. $C_{20}H_{19}O_3N_3$ requires C, 68·8; H, 5·5; N, 12·0%).

(*b*) 2-Naphthol (40 g.; 1 mol.), light petroleum (150 c.c.), *tert.*-butyl chloride (54 g.; 3 mols.), and anhydrous aluminium chloride (5 g.; 0·2 mol.) at 50—60° for 5 hours also gave (IV) (12 g.), m. p. 119—120° (confirmed by picrate), and its *tert.*-butyl ether (21 g.), m. p. 138°, not depressed on admixture with the products obtained by method (*a*).

(*c*) 2-Naphthol (30 g.), phosphoric acid (*d* 1·75; 65 c.c.), and *tert.*-butyl alcohol (20 g.), stirred at 95° for 3 hours and then at 100—110° for 4 hours, afforded (IV) (8 g.) and its *tert.*-butyl ether (12 g.).

1-*Amino*-2-*hydroxy*-4(?)-tert.-*butylnaphthalene*.—1-*p*-Nitrobenzeneazo-4(?)-*tert*.-butyl-2-naphthol (15 g.), m. p. 250—253°, was reduced with boiling aqueous-alcoholic sodium hydrosulphite (dithionite) for 4 hours; removal of alcohol and cooling gave the *amino-naphthol*, which crystallised from benzene in pale yellow plates, decomp. 150° (Found: C, 77·6; H, 7·7; N, 7·0. $C_{14}H_{17}ON$ requires C, 78·1; H, 7·9; N, 6·5%).

Oxidation of Di-tert.-*butylnaphthalene*, m. p. 145—146°.—Chromium trioxide (44 g.) in acetic acid (80 g.) and water (40 c.c.) was added to a stirred solution of the di-*tert*.-butylnaphthalene (22 g.) in acetic acid (200 c.c.); reaction was vigorous, and after boiling under gentle reflux for one hour, the mixture was added to ice; the precipitate (15 g.) was collected and crystallised from alcohol in pale yellow leaflets, m. p. 83—84°, of a steam-volatile di-*tert*.-butyl-1 : 4-naphthaquinone (Found: C, 79·8; H, 8·1. Calc. for $C_{18}H_{12}O_2$: C, 79·7; H, 8·1%) (cf. Price *et al.*, *loc. cit.*, who record m. p. 83—83·5°), which does not give a quinoxaline derivative with *o*-phenylenediamine in acetic acid (*e.g.*, *o*-quinones), but affords a *phenylhydrazone*, red needles (from alcohol), m. p. 188° (Found: C, 80·2; H, 7·7; N, 8·0. $C_{24}H_{22}ON_2$ requires C, 80·0; H, 8·0; N, 7·7%). With boiling acetic acid (8 c.c.), acetic anhydride (30 c.c.), anhydrous sodium acetate (2 g.), and zinc dust (3 g.), 3 g. of quinone gave 2·5 g. of 1 : 4-diacetoxydi-*tert*.-butylnaphthalene, which crystallised from light petroleum in colourless needles, m. p. 133° (Found: C, 74·0; H, 7·7. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9%) (Price *et al.* record m. p. 139—140°). Oxidation of the quinone (10 g.) was carried out by suspending it in water (300 c.c.) and adding a solution of potassium permanganate (20 g.) in water (600 c.c.) to the stirred mixture during 3 hours. After boiling for a total of 8 hours, excess of permanganate was destroyed and the mixture made alkaline with sodium hydroxide. It was then filtered and the filtrate (charcoaled) acidified with hydrochloric acid and extracted with ether; the ether extract was dried (Na_2SO_4) and after removal of ether, the oily residue (5 g.) was dissolved in hydrogen peroxide (5 c.c.; 100 vols.) and aqueous sodium hydroxide (25 c.c.; 10%) and left for 12 hours at room temperature. Ether extraction gave an oily residue which was boiled with light petroleum for 10 minutes, this separating the product into an insoluble colourless solid and a filtrate which yielded a sour-smelling oil. The solid was crystallised several times from chloroform–light petroleum to give colourless cubes (0·8 g.), m. p. 184—185°, the analysis agreeing with that required for a di-*tert*.-butylphthalic acid (Found: C, 69·3; H, 7·6. $C_{16}H_{22}O_4$ requires C, 69·1; H, 7·9%), but which gave an oil on boiling with acetic anhydride.

Oxidation of Di-tert.-*butylnaphthalene*, m. p. 85—90°.—The di-*tert*.-butylnaphthalene (5 g.), regenerated from its picrate, was boiled with chromic acid (10 g.), acetic acid (80 c.c.), and water (25 c.c.) for one hour, and gave a sticky yellow quinone, which could not be crystallised. It gave a *phenylhydrazone*, orange-red needles (from alcohol), m. p. 178—180° (Found: C, 79·4; H, 7·7; N, 7·6. $C_{24}H_{22}ON_2$ requires C, 80·0; H, 8·0; N, 7·7%), which depressed the m. p. of the isomer described above to 165—170°. The crude quinone was converted by reductive acetylation into colourless needles, m. p. 114—120° rising on repeated crystallisation from light petroleum to 132—133°, which on admixture with the diacetoxy-derivative described above showed no depression in m. p. The crude quinone was further oxidised as above to give colourless needles (from chloroform–light petroleum), m. p. 129—130° (Found: C, 62·8; H, 6·5. Calc. for $C_{13}H_{14}O_5$: C, 62·4; H, 5·6%), possibly of a mono-*tert*.-butylphthalonic acid.

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425. *Some Observations on Salts of Amidines and Related Compounds.*

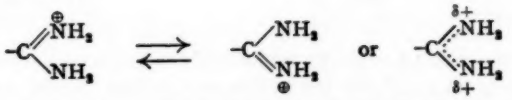
By JAMES WALKER.

Carboxylic acids are of value for the characterisation of *unsubstituted* amidines, and *vice versa*. A possible mechanism by which substances containing an unsubstituted amidino-group readily form highly crystalline salts with certain acids, especially carboxylic acids, is discussed and several extensions are mentioned.

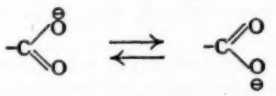
IN a previous paper (Fuller, Tonkin, and Walker, *J.*, 1945, 633) it was stated that, where crystallisation of the hydrochlorides of amidines unsubstituted in the amidine group proved difficult because of excessive solubility, double decomposition with sodium benzoate afforded much less soluble benzoates. This device, using both benzoates and acetates, has been found invaluable in a number of cases (Walker, *J.*, 1947, 1684; Forrest, Fuller, and Walker, *J.*, 1948, 1501; Forrest and Walker, *ibid.*, p. 1939) for the ready isolation of highly crystalline salts of amidines, and further consideration of the factors involved appears to be warranted. Carboxylic acid salts of amidines are not new substances and a number were prepared by Pinner ("Die Imidoäther und ihre Derivate," Berlin, 1892), incidental to his researches on imino-ethers and amidines, and one may note, in passing, that the so-called iminohydrins, or *iso*amides, of Eschweiler (*Ber.*, 1897, **30**, 998; Hantzsch and Voegelen, *ibid.*, 1901, **34**, 3142) proved to be carboxylic acid salts of amidines (Rule, *J.*, 1918, **113**, 3), but no systematic application of these salts has hitherto been developed. Complementary to the author's use of salts of carboxylic acids for the characterisation of unsubstituted amidines is the use of salts of unsubstituted amidines for the characterisation of carboxylic acids. The latter is, of course, similar to the familiar application of *S*-benzylthiuronium chloride (Donleavy and Johnson, *Science*, 1923, **57**, 753; Rugeley and Johnson, *J. Amer. Chem. Soc.*,

1925, **47**, 2995; Anderson, *J. Biol. Chem.*, 1927, **74**, 548; Donleavy, *J. Amer. Chem. Soc.*, 1936, **58**, 1004; Veibel and Lillelund, *Bull. Soc. chim.*, 1938, **5**, 1153; Veibel and Ottung, *ibid.*, 1939, **6**, 1434) and of its *p*-chloro- (Dewey and Sperry, *J. Amer. Chem. Soc.*, 1939, **61**, 3251), *p*-bromo- (Dewey and Shasky, *ibid.*, 1941, **63**, 3526), and *p*-nitro-derivatives (Rupe and Zweidler, *Helv. Chim. Acta*, 1940, **23**, 1025), and also of *S*-1-naphthylmethylthiuronium chloride (Bonner, *J. Amer. Chem. Soc.*, 1948, **70**, 3508) for the characterisation of carboxylic acids, since the salt-forming amidino-group is common to amidines and *iso*thioureas; amidines, however, are superior to *iso*thioureas for this purpose as they are stronger bases and recovery of the carboxylic acid is cleaner when amidines are employed, there being no danger of contamination with other acidic products such as is found when thiuronium salts are used (Anderson, *loc. cit.*; Kass, Nichols, and Burr, *J. Amer. Chem. Soc.*, 1942, **64**, 1061; Veibel and Lillelund, *loc. cit.*). Beyond the fact that *S*-benzylthiuronium salts have an established use in the laboratory for the characterisation of carboxylic acids, and also of sulphonic (R. F. Chambers and Scherer, *Ind. Eng. Chem.*, 1924, **16**, 1272; E. Chambers and Watt, *J. Org. Chem.*, 1941, **6**, 376) and sulphinic acids (Hann, *J. Amer. Chem. Soc.*, 1935, **57**, 2166), it does not appear that any significance, particularly of a theoretical kind, has been attached to this property of the amidino-group of forming highly crystalline, and often sparingly soluble, salts with certain acids.

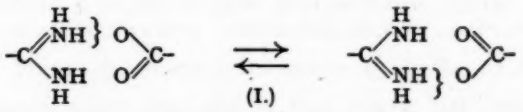
The constitution of salts of *S*-alkyl*iso*thioureas was discussed by Taylor (*J.*, 1917, **111**, 650; 1920, **117**, 4) in terms of ideas then still prevailing, and Lecher and his collaborators (*Annalen*, 1924, **438**, 154, 169; 1925, **445**, 35), who introduced the term "thiuronium," advanced the views acceptable at the present time as to the constitution of these salts, and also of those of amidines and *O*-alkyl*iso*ureas, in so far as the *kations* are concerned; these contain the resonating system



to which is ascribable the basic strength of these substances. With due acknowledgment to the earlier views of Hantzsch (*Ber.*, 1917, **50**, 1422), Lecher *et al.* (*Annalen*, 1925, **445**, 35) also presented the interpretation of the carboxylate ion acceptable at present, largely on the basis of the formal analogy between the amidinium group and the carboxylate ion, but they did not have occasion to discuss salts formed between the two. In considering now the behaviour



of the carboxylic acid salts of amidines, *iso*thioureas, or *iso*ureas, it is to be noted that the resonance in the kation is complementary to that in the anion, and it is suggested that ionic bonds are formed *simultaneously* between the two oxygen atoms sharing the negative charge in the carboxylate ion and the two nitrogen atoms sharing the positive charge in the amidinium group. Furthermore, the coplanarity of the *seven* atoms comprising the amidinium group, arising as a consequence of resonance stabilisation (cf. Mills, *J.*, 1943, 194), leads to (I) as a representation of the amidine salt of a carboxylic acid, in which the seven atoms of the amidinium group, the three atoms of the ionised carboxyl group, and the respective atoms to which these groups are linked, *i.e.*, twelve atoms altogether, are coplanar and assume a relatively rigid configuration of minimum potential energy, the implicit hydrogen bonds being short and relatively strong. Such association *in solution* into doublet ion-pairs of a relatively



(I.)

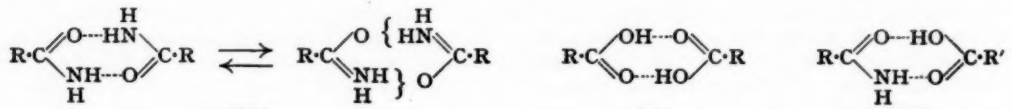
rigid oriented type is considered to be the prelude to the formation of crystalline aggregates, which proceeds by hydrogen bonding between the lateral amidinium hydrogen atoms and the oxygen atoms of the carboxylate groups in neighbouring doublet ion-pairs. It is obvious that purely chemical studies cannot supply the proof of these suggestions, and *X*-ray diffraction evidence is being sought. A survey of the literature, summarised in the form of a histogram, shows that the melting points of an extensive and heterogeneous range of *S*-benzyl-,

p-substituted *S*-benzyl-, and *S*-1-naphthylmethyl-thiuronium salts of carboxylic acids cover only a small range of temperature, which suggests that the forces which bind crystals of this type together are comparable in strength throughout the series and that the radicals attached to the $-S\cdot C(NH_2){:}\overset{\oplus}{N}H_2$ and $-C(:O)\cdot\overset{\ominus}{O}$ groups respectively make little or no contribution to the stability of the crystal; furthermore, it is exceptional to find such a salt of a carboxylic acid containing water of crystallisation. On the other hand, the sulphonic acid salts of the same bases show a more random distribution of melting point and occasionally contain water of crystallisation. In extension of the views developed above in advancing (I) this would be expected, since the anions of sulphonic acids are triply degenerate, while the amidinium group is doubly degenerate. The dissimilarity in the degree of degeneracy in this case allows of greater latitude on the part of the sulphonate ion in the organisation of the crystal including the hydrogen bonding involved in the incorporation of water of crystallisation. Data are lacking for a similar survey of amidine salts but the amidine salts of carboxylic acids appear to have higher melting points than those found for *S*-benzylthiuronium salts.

On the basis of (I) a reasonable interpretation can be advanced for the failure of substituted amidines to form crystalline salts with carboxylic acids with any degree of ease. Mono-substituted (*e.g.*, *N*-methyl) amidinium ions would, on resonance theory, be expected to exist in *syn*- (II) and *anti*- (III) forms, the resonance energy being a measure of the torsional rigidity of the C–N link (cf. Mills, *loc. cit.*). In the case of (II) the alkyl group inhibits sterically the

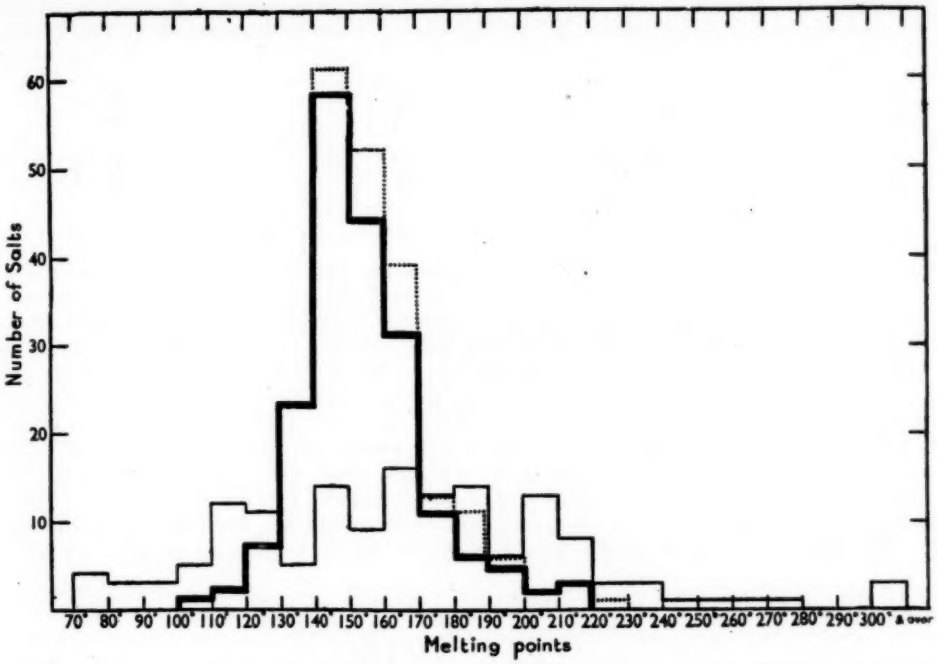
formation of a doublet ion-pair of type (I), while (III) could form a doublet ion-pair of type (I) with only *one* hydrogen atom available for hydrogen bonding, whereas *two* are required for the progressive formation of the crystal, as in diketopiperazine (Corey, *J. Amer. Chem. Soc.*, 1938, **60**, 1598); analogous considerations are applicable to the reduced association found in amides on *N*-substitution as shown by infra-red absorption spectra (Buswell, Downing, and Rodebush, *ibid.*, 1940, **62**, 2759). Incidentally, the structure (I), developed above, is formally reminiscent of the association of amides (IV) and of the well-known dimerisation of carboxylic acids (V), similar considerations being applicable to the products formed from amides and carboxylic acids (VI) (Topin, *Ann. Chim. Phys.*, 1896, **5**, 99; Titherley, *J.*, 1904, **85**, 1673; Henle, *Ber.*, 1905, **38**, 1373).

It is obvious that acids other than carboxylic acids should be capable of forming salts with the amidino-group to which analogous considerations could be applied. Particularly interesting examples are to be found in the reaction between nitrous acid and substances containing this



group; thus, benzamidine reacts with nitrous acid in the presence of excess of hydrochloric acid to give a dinitroso-derivative, " Benzenyldioxytetrazotsäure," which has acidic properties and separates from solution in the reaction in which it is produced in the form of its salt with unchanged benzamidine (Lossen, *Annalen*, 1891, **263**, 82), analogous behaviour being shown by *S*-aryl*iso*thioureas (Arndt, *Annalen*, 1913, **396**, 1) and by *S*-alkyl*iso*thioureas (Backer and Stedehouder, *Rec. Trav. chim.*, 1933, **52**, 923, 1039). In each case the acid, $R\cdot C(:N\cdot N:O)\cdot N:N\cdot OH$ or $R\cdot C(:N\cdot N:O)\cdot NH\cdot N:O$, affords a symmetrical resonating anion, $R\cdot C(:N\cdot N:O)\cdot N:N\cdot\overset{\ominus}{O}$ or $R\cdot C(:N\cdot N:O)\cdot\overset{\ominus}{N}\cdot N:O$, and the crystal unit of the salts which separate from the reaction mixtures can be represented as (VII); indeed, Arndt (*loc. cit.*) succeeded in converting the *S*-*p*-tolyl*iso*thiourea salt of dinitroso-*S*-*p*-tolyl*iso*thiourea, *via* the potassium salt, into the benzamidine salt.

Any anion capable of providing suitably situated alternative positions for the negative charge and having a resonance energy, and hence a resonance frequency, similar to that of the amidinium group might be expected to undergo with the latter ionic association similar to



Distribution of m. p.s of S-*benzyl-*, S-p-*chlorobenzyl-*, S-p-*bromobenzyl-*, *and* S-p-*nitrobenzyl-thiuronium salts of* 193 *carboxylic* (——) *and of* 149 *sulphonic* (——) *acids.*

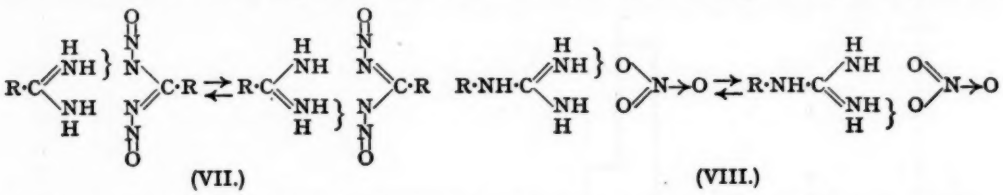
Mean m. p. of carboxylic acid salts, 154°, *with a standard deviation of* 18°; *mean m. p. of sulphonic acid salts,* 165°, *with a standard deviation of* 46°.

The dotted additions to the carboxylic acid columns comprise the S-1-*naphthylmethylthiuronium salts of* 28 *carboxylic acids.*

Data from: *Anderson*, loc. cit.; *Archer* et al., J. Amer. Chem. Soc., 1945, **67**, 43; *Bair and Suter*, ibid., 1942, **64**, 1978; *Baker and Carlson*, ibid., *p.* 2657; *Baker* et al., ibid., *p.* 1096; *Baker* et al., J. Org. Chem., 1947, **12**, 186; *Bergel* et al., J., 1944, 415; *Bonner*, loc. cit.; *Bordwell* et al., J. Amer. Chem. Soc., 1946, **68**, 139; 1945, **67**, 827; *Caldwell and Kornfeld*, ibid., 1942, **64**, 1695; *Campaigne and Suter*, ibid., *p.* 3040; ibid., 1946, **68**, 880; *Chambers and Scherer*, loc. cit.; *Chambers and Watt*, loc. cit.; *Chodroff, Kapp, and Beckmann*, J. Amer. Chem. Soc., 1947, **69**, 256; *Christian and Jenkins*, J. Amer. Pharm. Assoc., 1945, **34**, 147; *Clemo and Legg*, J., 1947, 539; *Clemo and Turnbull*, J., 1947, 124; *Cocker*, J., 1946, 36; *Dewey and Shasky*, loc. cit.; *Dewey and Sperry*, loc. cit.; *Donleavy*, loc. cit.; *Emerson and Smith*, J. Amer. Chem. Soc., 1940, **62**, 1869; *English and Cavaglieri*, ibid., 1943, **65**, 1085; *Fierz-David* et al., Helv. Chim. Acta, 1946, **29**, 1718; *Gaunt* et al., J. Soc. Dyers Col., 1947, **63**, 48; *Gripenberg*, Ann. Acad. Sci. Fennicae, 1943, A, **59**, *No.* 14, 7; *Hann*, loc. cit.; *Hann and Keenan*, J. Physical Chem., 1927, **31**, 1084; *Hardegger*, Helv. Chim. Acta, 1946, **29**, 1195; *Hardegger* et al., ibid., 1945, **28**, 628; *Haynes and Jones*, J., 1946, 503; *Hennion and Schmidle*, J. Amer. Chem. Soc., 1943, **65**, 2468; *Huber* et al., ibid., 1945, **67**, 1148; *Kass* et al., loc. cit.; *Kimura and Taniguti*, J. Soc. Chem. Ind. Japan, 1939, **42** (*Supp.*), 234; *Komori and Ueno*, Bull. Chem. Soc. Japan, 1937, **12**, 433; *Kratzl*, Ber., 1943, **76**, 895; 1944, **77**, 717; *Kratzl and Däubner*, ibid., *p.* 519; *Leonard and Spoerri*, J. Amer. Chem. Soc., 1946, **68**, 526; *Levey and Lewis*, J. Biol. Chem., 1947, **168**, 213; *McPhee and Klingsberg*, J. Amer. Chem. Soc., 1944, **66**, 1132; *McPhee and Lindstrom*, ibid., 1943, **65**, 2177; *B.P.* 567,438; *U.S.P.* 2,337,576; *Plattner* et al., Helv. Chim. Acta, 1946, **29**, 730; *Pucher and Vickery*, J. Biol. Chem., 1946, **163**, 169; *Rugeley and Johnson*, loc. cit.; *Ruggli and Dahn*, Helv. Chim. Acta, 1944, **27**, 867; *Rupe and Frey*, ibid., *p.* 627; *Rupe and Zweidler*, loc. cit.; *Schenkel* et al., Helv. Chim. Acta, 1944, **27**, 1437; *Schmid and Karrer*, ibid., 1945, **28**, 722; *Seidel* et al., ibid., 1944, **27**, 663; *Shoppee and Reichstein*, ibid., 1942, **25**, 1611; *Smith and Rouault*, J. Amer. Chem. Soc., 1943, **65**, 745; *Snyder and Handrick*, ibid., 1944, **66**, 1860; *Soper* et al., ibid., 1948, **70**, 2849; *Stiller* et al., ibid., 1940, **62**, 1785; *Suter* et al., J. Org. Chem., 1945, **10**, 470; *Suter and Bordwell*, J. Amer. Chem. Soc., 1943, **65**, 507; *Suter* et al., ibid., 1941, **63**, 1594; *Suter and Milne*, ibid., 1943, **65**, 582; *Suter and Truce*, ibid., 1944, **66**, 1105; *Taylor*, loc. cit.; *Urist and Jenkins*, J. Amer. Chem. Soc., 1941, **63**, 2943; *Veibel*, ibid., 1945, **67**, 1867; *Veibel and Lillelund*, loc. cit.; *Veibel and Ottung*, loc. cit.; *Vischer and Reichstein*, Helv. Chim. Acta, 1944, **27**, 1332; *v. Wacek*, Ber., 1944, **77**, 85; *v. Wacek and Kratzl*. ibid., 1943, **76**, 1209; *v. Wacek* et al., ibid., 1942, **75**, 1348; *Whitmore and Landau*, J. Amer. Chem. Soc., 1946, **68**, 1797; *Work*, J., 1947, 222.

Where the same salt has been described by more than one group of authors, the mean m. p. was taken, when the individual observations agreed to within a few degrees; in a few cases where the m. p.s of a salt, recorded by different observers, showed considerable divergence, that salt was omitted from the survey.

(I). In a similar manner, the excellence of nitrates for the isolation and characterisation of substituted guanidines, long known in the laboratory, may be interpreted by the formation



(VII.) (VIII.)

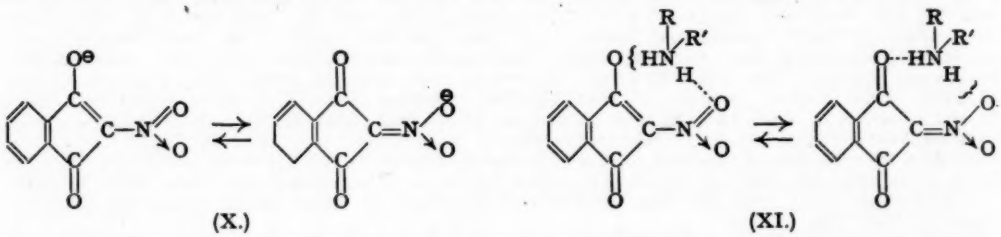
in solution of (VIII) from which the crystal is thereafter progressively built up; nitrates are also useful for the characterisation of amidines, several examples being recorded below. On the basis of (I), dibasic acids of the type H_2XO_4 should provide with amidines normal salts of the type (IX) with the atom X in a tetrahedral environment at a centre of symmetry. These are exemplified by the preparation of *benzamidinium chromate* and *tetrahydrogeranamidinium sulphate*; an attempt to prepare tetrahydrogeranamidinium hydrogen sulphate by double decomposition yielded the normal sulphate instead, and similar behaviour has been observed with *S*-benzylthiuronium hydrogen sulphate, which passed readily into the normal sulphate on recrystallisation from water (Lecher *et al.*, *Annalen*, 1925, **445**, 58). Thiosulphates would be expected to show similar behaviour, and benzamidinium thiosulphate and *tetrahydrogeranamidinium thiosulphate* have been prepared; the former has been described by Crayen (*Ber.*, 1891, **24**, 385), who obtained it in a remarkable transformation by allowing the product

(IX.)

from the reaction of carbon disulphide with benzamidoxime to decompose in air at 100°, recalling the formation of phenylacetamidinium thiosulphate by the action of air on an alcoholic solution of phenylacetothioamide (Bernthsen, *Annalen*, 1877, **184**, 321).

The essential feature of structure (I) is that the anion and kation hold each other electrostatically and rigidly in a preferred orientation, and this behaviour may well underlie the activities of amidines, guanidines, *iso*thioureas, and *iso*ureas as drugs, since Fastier (*Nature*, 1944, **154**, 429; *Brit. J. Pharmacol.*, 1948, **3**, 198; Fastier and Smirk, *J. Pharm. Exp. Ther.*, 1947, **89**, 256) has shown that these substances, besides showing close analogies in their chemical behaviour, form a single well-defined pharmacological group in addition to the well-known chemotherapeutic activity of individual compounds. In these cases the resonating acidic group forming ionic bonds with the amidino-group in the drug may be identified with functional groups in the cellular structures affected by the drugs in question. It should be borne in mind also that in nucleoproteins there is essentially a salt-like union of nucleic acid with a basic protein and that it may be with this type of linkage that chemotherapeutic agents of the amidine type exert their action.

It seems worth while to consider in this connexion, too, the property of 2-nitroindane-1 : 3-dione of readily forming rather sparingly-soluble salts with primary and secondary amines, but not with tertiary amines (Wanag, *Ber.*, 1936, **69**, 1066; *J. Gen. Chem. Russia*, 1947, **17**, 2080; Wanag and Lode, *Ber.*, 1937, **70**, 547). As a working hypothesis the author would



(X.) (XI.)

suggest that the anion (X) in virtue of resonance has the power of forming rigid ion-pairs (XI) with the kations of *primary* and *secondary* amines, which have *two* hydrogen atoms

available for hydrogen bonding, and that the crystal is thereafter progressively built up from mutually oriented ion-pairs; kations of *tertiary* amines having but *one* hydrogen atom attached to nitrogen cannot form ion-pairs of type (XI). Here again, orthodox methods of organic chemistry cannot supply proof or disproof of this theory and it would be helpful to have *X*-ray diffraction evidence. While the discrimination of 2-nitroindane-1 : 3-dione between primary and secondary bases on the one hand and tertiary bases on the other is sharply defined, a similar trend is discernible with dilituric acid (5-nitrobarbituric acid) (Redemann and Niemann, *J. Amer. Chem. Soc.*, 1940, **62**, 590), which might be expected to show similar behaviour. The dilituric acid of representative primary and secondary amines are sparingly soluble salts, while those of tertiary bases are much more soluble; a few heterocyclic bases, however, afford sparingly soluble dilituric acid.

The experimental portion of this communication describes a number of salts of amidines and related compounds prepared and examined in the light of the considerations outlined above, separation of a crystalline solid phase on double decomposition in cold fairly concentrated aqueous solution being used as a criterion of ready crystallisation. To illustrate the effects of substitution in the amidine group on the crystallisation of salts, benzamidine hydrochloride, 2-phenyldihydroglyoxalinium chloride, and 2-phenylglyoxalinium nitrate were studied; only benzamidine hydrochloride yielded a benzoate and an acetate under the standard conditions, and neither of the other two bases afforded crystalline salts of simple carboxylic acids. *2-Phenylglyoxalinium* p-*nitrobenzoate* was obtained readily in a highly crystalline condition, the nitro-group doubtless facilitating crystallisation, and it should be noted that Fargher and Pyman (*J.*, 1919, **115**, 217) record several cases of crystalline hydrogen oxalates in the glyoxaline series, where the second carboxyl group has undoubtedly a powerful influence. As a substituted analogue of *S*-benzylthiuronium chloride and one which would still be markedly basic, *2-benzylthiodihydroglyoxalinium chloride* was prepared and found to lack entirely the capacity of the former salt to yield precipitates with aqueous solutions of the sodium salts of a number of carboxylic acids.

As it appeared probable that a branched-chain aliphatic amidine might show some activity against the tubercle bacillus (cf. Buu-Hoï, *Nature*, 1945, **156**, 392; also Newbery and Webster, *J.*, 1947, 738), tetrahydrogeranamidinium sulphate was kindly tested *in vitro* by Dr. D'Arcy Hart against *M. tuberculosis* and against *M. phlei*, but the observed activity was not of a high order.

Experimental.

General Method for the Preparation of Salts by Double Decomposition.—Concentrated cold aqueous solutions of base hydrochloride (or other salt) (0·001—0·01 g.-mol.) and the sodium, potassium, or ammonium salt of the carboxylic (or other) acid (1·1 equivs.) were mixed, crystallisation being induced, if necessary, by scratching. Water was added, if necessary, in sufficient amount to give a clear solution at the b. p. and, after cooling, the crystals were collected and crystallised to constant m. p., one recrystallisation usually sufficing. The solubility gradients are usually such that quite small volumes of solvent are required for recrystallisation, and yet little loss is experienced if suitable methods are used.

p-*Methylsulphonylbenzamidinium acetate* crystallised from 3 parts of water in stellate clusters of colourless rectangular prisms, m. p. 236—237° (efferv.) (Found: C, 46·7; H, 5·3; N, 10·8. $C_9H_{10}O_2N_2S,C_2H_4O_2$ requires C, 46·5; H, 5·4; N, 10·9%). p-*Methylsulphonylbenzamidinium nitrate* separated from 2 parts of water in stout colourless prisms, m. p. 208—209° (Found: N, 16·0. $C_9H_{10}O_2N_2S,HNO_3$ requires N, 16·1%). p-*Sulphonamidobenzamidinium benzoate* crystallised from 5 parts of water in long fine needles, m. p. 231—232° (Found: C, 52·1; H, 4·6; N, 13·1. $C_7H_9O_2N_3S,C_7H_6O_2$ requires C, 52·3; H, 4·7; N, 13·1%). p-*Sulphonamidobenzamidinium acetate* crystallised from 3 parts of water in stellate clusters of colourless rectangular prisms, m. p. 227—228° (Found: C, 41·5; H, 4·9; N, 15·9. $C_7H_9O_2N_3S,C_2H_4O_2$ requires C, 41·7; H, 5·0; N, 16·2%). p-*Sulphonamidobenzamidinium nitrate* separated from 2 parts of water in small stout prisms, m. p. 195—196° (Found: N, 19·8, 19·8. $C_7H_9O_2N_3S,HNO_3,H_2O$ requires N, 20·0%). Benzamidinium benzenesulphonate crystallised from rather more than one part of water in colourless thin plates, nearly rectangular in outline, m. p. 175—176° (Found: N, 10·1. Calc. for $C_7H_8N_2,C_6H_6O_3S$: N, 10·2%); Rouiller (*Amer. Chem. J.*, 1912, **47**, 475) records m. p. 173°, and Oxley and Short (*J.*, 1946, 147) record m. p. 175—175·5°. Benzamidinium thiosulphate separated from 2 parts of water in large, thin, transparent, hexagonal plates, m. p. 217° (decomp.) (Found: N, 16·0. Calc. for $2C_7H_8N_2,H_2S_2O_3$: N, 15·8%); Crayen (*loc. cit.*) records m. p. 222°. *Benzamidinium chromate* crystallised from about 8 parts of water in stout canary-yellow rhombs, m. p. 184° (decomp.) (Found: C, 46·9; H, 5·3; N, 15·6. $2C_7H_8N_2,H_2CrO_4$ requires C, 46·9; H, 5·0; N, 15·6%). S-*Methylthiuronium benzoate* crystallised from about 12 parts of water in colourless rectangular prisms, m. p. 184—185° (efferv.) (Found: N, 13·4. $C_2H_6N_2S,C_7H_6O_2$ requires N, 13·2%). *O*-Methyluronium salicylate crystallised from 0·8 part of water in fine prisms, m. p. 138—139° (Found: N, 13·3. Calc. for $C_2H_6ON_2,C_7H_6O_3$: N, 13·2%); Basterfield and Powell (*Canadian J. Res.*, 1929, **1**, 261) record m. p. 128°. *Guanidinium benzoate* crystallised from 1·5 parts of water in fine, colourless, obliquely-terminated prisms, attaining lengths up to 3 cm., m. p. 225—226° (Found: N, 23·0. $CH_5N_3,C_7H_6O_2$ requires N, 23·2%). 2-*Phenyl-*

glyoxalinium p-*nitrobenzoate* crystallised from about 30 parts of water in fine silky needles, m. p. 166° (Found : N, 13·8. $C_9H_8N_2,C_7H_5O_4N$ requires N, 13·5%); the unsubstituted benzoate was precipitated as a gum which did not crystallise in the course of several months.

Tetrahydrogeranamidine Hydrochloride.—(i) Technical citronellal (46·5 g.) was hydrogenated in methyl alcohol (200 c.c.) in the presence of 2% palladised strontium carbonate (5 g.) with hydrogen at 3 atm. pressure. Hydrogenation proceeded slowly and was complete in about 12 hours. Dihydrocitronellal (31 g.), b. p. 100—104°/26 mm., was obtained on fractionation of the product. The aldehyde (28 g.) was treated with hydroxylamine hydrochloride (13 g.) and sodium acetate crystals (25·5 g.) in aqueous alcohol (to homogeneity) in the cold for 48 hours. The resulting product, isolated by pouring into water and extraction with ether, afforded the oxime (25·4 g.), b. p. 128—134°/25 mm., which was then heated under reflux with acetic anhydride (100 c.c.) for an hour; the tetrahydrogeranonitrile (19 g.), b. p. 115°/25 mm., obtained on fractionating the product gave somewhat low values for nitrogen but it was sufficiently pure for conversion into the amidine.

(ii) A mixture of tetrahydrogeranonitrile (45·7 g.) and absolute alcohol (70 c.c.) was saturated with dry hydrogen chloride at 0° and the solution was kept for a week in the ice-chest. Solvent and excess of hydrogen chloride were removed in a vacuum and the resulting syrup was set aside in a pressure bottle with 10% alcoholic ammonia solution for several days at 37°. The solution was then filtered and evaporated to dryness. The residue was taken up in water, giving a clear solution becoming turbid on continued addition of water. The diluted solution was extracted several times with ether and the aqueous layer was then evaporated to dryness. The residue was exhaustively dried by repeated extraction with absolute alcohol and evaporation of the extract to dryness. The product (35·1 g.) then crystallised slowly. Crystallisation from dry acetone afforded small colourless leaflets of *tetrahydrogeranamidine hydrochloride*, m. p. 95—96·5° (Found : N, 13·3. $C_{10}H_{22}N_2,HCl$ requires N, 13·6%).

Tetrahydrogeranamidinium benzoate crystallised from about 70 parts of water in pearly plates, m. p. 189° (Found : N, 9·4. $C_{10}H_{22}N_2,C_7H_6O_2$ requires N, 9·6%). The *sulphate* crystallised from about 70 parts of water in plates, m. p. 291° (decomp.) (Found : C, 54·3; H, 10·3; N, 13·0. $2C_{10}H_{22}N_2,H_2SO_4$ requires C, 54·7; H, 10·5; N, 12·8%). The normal sulphate (Found : N, 13·0%) was obtained when an attempt was made to prepare the hydrogen sulphate. The *thiosulphate* crystallised from about 70 parts of water in plates, m. p. 221° (decomp.) (Found : N, 12·4. $2C_{10}H_{22}N_2,H_2S_2O_3$ requires N, 12·3%). The *nitrate* crystallised from about 40 parts of water in pearly plates, m. p. 152—153° (Found : N, 18·0. $C_{10}H_{22}N_2,HNO_3$ requires N, 18·0%).

2-Benzylthiodihydroglyoxalinium Chloride.—An alcoholic solution of ethylenethiourea (5·6 g.) (Johnson and Edens, *J. Amer. Chem. Soc.*, 1942, **64**, 2706) and benzyl chloride (6·7 g.) was heated under reflux for several hours and the solvent was then distilled off. The *product* separated from a small volume of *iso*propyl alcohol in small stout prisms (10 g.), m. p. 145—145·5° (Found : N, 12·4. $C_{10}H_{12}N_2S,HCl$ requires N, 12·3%).

2-Phenyldihydroglyoxalinium Chloride.—2-Phenyldihydroglyoxaline was obtained in good yield from benziminoethyl ether hydrochloride and ethylenediamine (cf. Austrian Patent 150,307), the base being isolated by ether extraction after the addition of excess of caustic alkali. Aspinall (*J. Org. Chem.*, 1941, **6**, 895) showed that 2-substituted iminazolines were readily hydrolysed by hot water to monoacylethylenediamines, and Hill and Aspinall (*J. Amer. Chem. Soc.*, 1939, **61**, 822) prepared the hydrochlorides of the former bases by passing dry hydrogen chloride into alcoholic solutions of the bases. It should be noted, however, that the ready hydrolysis of the free bases in hot water is what would be expected in amidines and that neutralisation with mineral acid affords salts that are quite stable to water. 2-Phenyldihydroglyoxalinium chloride was obtained by dissolving the free base in spirit, adding a slight excess of N-hydrochloric acid, and evaporating the solution to dryness on the water-bath. The chloride crystallised from *iso*propyl alcohol in short stout prisms, m. p. 234°; Hill and Aspinall (*loc. cit.*) record m. p. 244° (corr.).

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426. *Reductone and the Synthesis of Pteridines.*

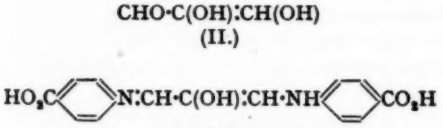
By H. S. FORREST and JAMES WALKER.

The possible rôle of reductone in the biosynthesis of pteroic acid and its use in the laboratory synthesis of pteridines are discussed. Possible antagonists of pteroylglutamic acid have been synthesised by condensing a number of sulphur-containing compounds severally with reductone in equimolecular proportions and then allowing the resulting 1 : 1 condensation products to react with 2 : 4 : 5-triamino-6-hydroxypyrimidine. The products from sulphanilylglycine and sulphanilyl-L-glutamic acid produced some inhibition of the growth of a strain of *Streptococcus lactis*.

IT has been pointed out in previous communications that the three-carbon atom unit (indicated in bold letters) comprising the ring atoms 7 and 6 and the exocyclic carbon atom of pteroic acid (I) might be provided biogenetically by a triose, and, in the first place, 3-phosphoglyceraldehyde and phosphodihydroxyacetone were indicated as possible precursors (Forrest and Walker, *Nature*, 1948, **161**, 308; this vol., p. 79). The suggestion, however, by O'Meara, McNally, and Nelson (*Nature*, 1944, **154**, 796; *Lancet*, 1947, II, 747) that reductone (II) might be the strongly reducing, non-thiol substance formed in a variety of bacterial cultures during the

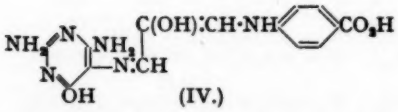
logarithmic phase of growth—the phase during which, incidentally, the antibacterial activity of the sulphonamides is maximal—suggested to us that this substance might well be our postulated triose precursor (Forrest and Walker, *Nature*, **1948**, **161**, 721; this vol., p. 79). O'Meara and his colleagues (*Lancet*, **1947**, II, 747) showed that streptococci could utilise the condensation product of (II) with *p*-aminobenzoic acid, but not free *p*-aminobenzoic acid, as a source of energy for growth, and it is noteworthy that Nimmo-Smith, Lascelles, and Woods (*Brit. J. Exp. Path.*, 1948, **29**, 264) have shown that only glucose, from which reductone is derivable (von Euler and Martius, *Annalen*, **1933**, **505**, 73), and *p*-aminobenzoic acid are required for the synthesis of folic acid by *Streptobacterium plantarum*, glutamic acid being merely stimulatory. O'Meara and his collaborators suggested that *p*-aminobenzoic acid acts as a stabilising agent for reductone in bacterial metabolism, enabling the cell to store reductone and to utilise it as required, presumably after hydrolysis of the reductone–*p*-aminobenzoic acid condensation product to free reductone, and they also suggested that sulphonamides interfere with bacterial growth by combining with reductone and preventing it from becoming available for the use of the cell. The possibility, however, presents itself that *p*-aminobenzoic acid and reductone are first linked together in normal bacterial metabolism and then incorporated into pteroic acid and other factors of the folic acid group, such as pteroylglutamic acid, whereas in sulphonamide bacteriostasis the drug combines with reductone and the condensation product is incorporated into a biologically inert—and perhaps even toxic—analogue of pteroic acid (Forrest and Walker, *Nature*, **1948**, **161**, 721). In other words, *p*-aminobenzoic acid and sulphonamides may compete, not for the service of an enzyme as required by the Woods–Fildes theory of sulphonamide bacteriostasis, but, chemically, for a strictly limited supply of pteridine precursors, and the development of sulphonamide resistance in bacteria may be brought about by enhanced production of these precursors in excess of normal requirements. In the light of these considerations the present work was undertaken to investigate the potentialities of reductone in the laboratory synthesis of pteroic acid and analogous substances.

Preliminary experiments, already reported (this vol., p. 79), were of two types. In the first type, the condensation product (III) formed in the reaction between one molecular proportion of reductone and two molecular proportions of *p*-aminobenzoic acid was first isolated and allowed to react with 2 : 4 : 5-triamino-6-hydroxypyrimidine under a variety of conditions. The products were directly oxidised and 2-amino-4-hydroxypteridine-7-carboxylic acid * was obtained in every case. That (III) was actually derived from *p*-aminobenzoic acid and (II) in the ratio 2 : 1 is borne out by further analytical data recorded below, and the constitution (III), involving terminal condensation on the part of the reductone, is borne out by the results of the experiments of the second type, in which reductone was added to a mixture of 2 : 4 : 5-triamino-6-hydroxypyrimidine and *p*-aminobenzoic acid, whereupon a rapid reaction took place. The products on oxidation again afforded 2-amino-4-hydroxypteridine-7-carboxylic acid. The course of this second type of reaction can best be interpreted by assuming reaction of reductone in the 1 and 3 positions with the amino-group of *p*-aminobenzoic acid and the reactive 5-amino-group of 2 : 4 : 5-triamino-6-hydroxypyrimidine respectively, giving (IV),

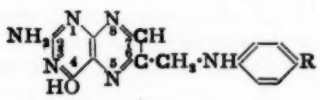


(II.)

(III.)



(IV.)



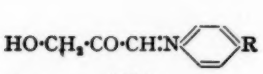
(I.) R = CO_2H
(XIV.) R = $SO_2{\cdot}NH_2$
(XV.) R = $SO_2{\cdot}CH_3$
(XVI.) R = $SO_2{\cdot}NH{\cdot}CH_2{\cdot}CO_2H$
(XVII.) R = $SO_2{\cdot}NH{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$
(XVIII.) R = $SO_2{\cdot}NH$–

which then cyclises to the 7-isomeride of pteroic acid. That reductone condenses with aromatic amines in the 1 and 3 positions when presented *simultaneously* with two molecular proportions of amine therefore appears to be clear. The valuable clue that reaction proceeds differently if reductone is allowed to react with only one molecular proportion of aromatic amine *before*

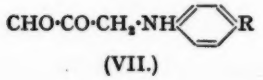
* The Ring Index numbering is now adopted, cf. (I). EDITOR.

the addition of the 2 : 4 : 5-triamino-6-hydroxypyrimidine was obtained by allowing reductone and methyl *p*-aminobenzoate to react with each other in equimolecular proportions for a short time before the addition of 2 : 4 : 5-triamino-6-hydroxypyrimidine, and the product in this case was pteroic acid (I); pteroic acid was also obtained when the 1 : 1 condensation product (V) of reductone with methyl *p*-aminobenzoate was first isolated and then allowed to react with 2 : 4 : 5-triamino-6-hydroxypyrimidine. In the previous communication (this vol., p. 79) it was pointed out that condensation reactions of 2 : 4 : 5-triamino-6-hydroxypyrimidine at the pH of our experiments must be initiated by nucleophilic attack by the amino-group in the 5-position on an electrophilic centre. We would therefore suggest that while the condensation product of reductone with methyl *p*-aminobenzoate is doubtless *methyl* p-(2 : 3-*dihydroxyprop*-2-*enylideneamino*)*benzoate* (V) initially, tautomeric equilibration to an anil of hydroxymethylglyoxal (VI; R = CO_2Me) takes place before the subsequent reaction with 2 : 4 : 5-triamino-6-hydroxypyrimidine, initiated at the 5-amino-group, and cyclisation to (I). That reductone itself is in tautomeric equilibrium with hydroxymethylglyoxal is obvious from the observations of Norrish and Griffiths (*J.*, 1928, 2829). At this point, as indicated in our preliminary note (*Nature*, 1948, **161**, 721), a communication from Angier and his collaborators appeared (*J. Amer. Chem. Soc.*, 1948, **70**, 25; also U.S.P. 2,442,836), describing the preparation of 1 : 1 condensation products of reductone with *p*-aminobenzoic acid and a number of its derivatives, those from *p*-aminobenzoic acid and its ethyl ester and from *p*-aminobenzoyl-L-glutamic acid and its diethyl ester being subsequently condensed with 2 : 4 : 5-triamino-6-hydroxypyrimidine to give pteroic acid and pteroylglutamic acid respectively. The American authors, however, do not appear to have appreciated the possible biogenetic significance of reductone. It also appears probable that they regarded the keto-aldehyde tautomer (VII) as the form undergoing reaction; this, it should be pointed out, would, in the case of (V), certainly react with 2 : 4 : 5-triamino-6-hydroxypyrimidine to give the 7-isomeride of pteroic acid and not pteroic acid (I), in the same way that methylglyoxal and 2 : 4 : 5-triamino-6-hydroxypyrimidine afford 2-amino-4-hydroxy-7-methylpteridine. Backer and Houtman (*Rec. Trav. chim.*, 1948, **67**, 260) have obtained 2-amino-4-hydroxy-7(?)-hydroxymethylpteridine by condensing 2 : 4 : 5-triamino-6-hydroxypyrimidine with hydroxymethylglyoxal in aqueous solution at the boiling-point but their attempt, carried out in the cold, to obtain the same substance, or the 6-hydroxymethyl isomer, from reductone and 2 : 4 : 5-triamino-6-hydroxypyrimidine failed to proceed beyond the unstable initial intermediate, although in our hands the same reaction gave on the water-bath a product affording 2-amino-4-hydroxypteridine-7-carboxylic acid on oxidation (this vol., p. 79).

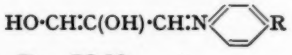
In accordance with the theory of sulphonamide bacteriostasis outlined above, sulphonamide drugs are pictured as being incorporated into biologically inert analogues of pteroic acid. Such analogues, however, would be likely to inhibit the growth of organisms requiring preformed factors of the folic acid group, such as pteroylglutamic acid; in other words, they would be antagonists of pteroylglutamic acid, although they would not be expected to inhibit markedly the growth of sulphonamide-sensitive organisms. Reductone was condensed in equimolecular proportions with sulphanilamide, *p*-methylsulphonylaniline, sulphanilylglycine, sulphanilyl-L-glutamic acid, diethyl sulphanilylglutamate, and sulphadiazine with the production of N^4-(2 : 3-*dihydroxyprop*-2-*enylidene*)*sulphanilamide* (VIII), p-(2 : 3-*dihydroxyprop*-2-*enylideneamino*)*phenyl methyl sulphone* (IX), N-p-(2 : 3-*dihydroxyprop*-2-*enylideneamino*)*benzenesulphonylglycine* (X), N-p-(2 : 3-*dihydroxyprop*-2-*enylideneamino*)*benzenesulphonylglutamic acid*

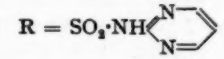


(VI.)



(VII.)



(V.) R = CO_2Me
(VIII.) R = $SO_2{\cdot}NH_2$
(IX.) R = $SO_2{\cdot}CH_3$
(X.) R = $SO_2{\cdot}NH{\cdot}CH_2{\cdot}CO_2H$
(XI.) R = $SO_2{\cdot}NH{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$
(XII.) R = $SO_2{\cdot}NH{\cdot}CH(CO_2Et){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$
(XIII.) R = $SO_2{\cdot}NH$ 

(XI), the *monoethyl* ester (XII) of (XI), and N^1-2-*pyrimidyl*-N^4-(2 : 3-*dihydroxyprop*-2-*enylidene*)-*sulphanilamide* (XIII). These condensation products were then in turn allowed to react with

2 : 4 : 5-triamino-6-hydroxypyrimidine, affording N^4-(2-*amino*-4-*hydroxy*-6-*pteridylmethyl*)*sulphanilamide* (XIV), p-(2-*amino*-4-*hydroxy*-6-*pteridylmethyl*)*aminophenyl methyl sulphone* (XV), N-p-(2-*amino*-4-*hydroxy*-6-*pteridylmethyl*)*aminobenzenesulphonylglycine* (XVI), N-p-(2-*amino*-4-*hydroxy*-6-*pteridylmethyl*)*aminobenzenesulphonylglutamic acid* (XVII), and N^1-2-*pyrimidyl*-N^4-(2-*amino*-4′-*hydroxy*-6′-*pteridylmethyl*)*sulphanilamide* (XVIII), respectively. In the ultimate analysis of these latter compounds the difficulties familiar in this field were again encountered (cf. Wieland and Purrmann, *Annalen*, 1940, **544**, 163), low carbon and high hydrogen values being obtained under ordinary conditions of drying and combustion. Recourse was therefore had to drying specimens at 140—160° before microanalysis, and under these conditions reasonably satisfactory results were obtained. Proof of the constitutions of (XIV)—(XVIII) was obtained by cleavage in aerated alkali, 2-amino-4-hydroxypteridine-6-carboxylic acid being formed in each case, and a further approximate analytical check on the compounds was obtained by colorimetric determination of the primary aromatic amine formed simultaneously.

Tests for *in vitro* activity against *Strep. hæmolyticus*, *Staph. aureus*, and *Bact. coli* were kindly carried out by Dr. A. T. Fuller on compounds (XIV)—(XVIII) but, as expected, none showed significant activity against these organisms, with the possible exception of (XIV) and (XV) which showed some activity in broth cultures of hæmolytic streptococci when the implants

Effect of (XVI) *and* (XVII) *on the growth of* Streptococcus lactis (N.C.T.C. 2700).

Concn. of pteroylglutamic acid. 10^{-9} g./c.c.	Concn. of drug. 10^{-6} g./c.c.	Turbidity * (Spekker). (XVI.)	(XVII.)
0	0	0·49	0·49
0·04	0	0·60	0·60
0·04	0·4	0·58	0·50
0·04	1·6	0·50	0·47
0·04	6·3	0·49	0·40
0·04	25	0·39	0·18
0·04	100	0·09	0·00
0·4	0	0·71	0·71
0·4	0·4	0·69	0·72
0·4	1·6	0·68	0·70
0·4	6·3	0·60	0·63
0·4	25	0·48	0·58
0·4	100	0·09	0·12

The basal medium used was that of Luckey, Briggs, and Elvehjem (*J. Biol. Chem.*, 1944, **152**, 157) except that sodium citrate was substituted for sodium acetate.

* Observed after incubation at 37° for 18 hours.

were small and growth was scanty. Compounds (XVI) and (XVII) were kindly examined in some detail by Miss J. M. Horton for activity against a strain of *Strep. lactis*. Both compounds inhibited the growth of this organism and the inhibition was reversed by pteroylglutamic acid; a representative series of observations is recorded in the Table. From these figures it does not appear that either compound can be regarded as a powerful antagonist of pteroylglutamic acid, but we have no basis of comparison with other known folic acid antagonists. Indeed, markedly different results would be expected with other strains of *Strep. lactis* as these vary widely in their folic acid requirements (cf. Stokes, Keresztesy, and Foster, *Science*, 1944, **100**, 522) and hence in their responses to folic acid antagonists. In view of the reported activity of folic acid antagonists in neoplastic growth, Professor Alexander Haddow kindly examined compounds (XIV), (XVII), and (XVIII) for activity on the Walker carcinoma 256 in the rat, but no inhibitory effect was observed.

Experimental.

p-(3-p′-*Carboxyanilino*-2-*hydroxyprop*-2-*enylideneamino*)*benzoic Acid* (III).—The product resulting from the condensation of one molecular proportion of reductone with two molecular proportions of *p*-aminobenzoic acid in hot dilute acetic acid solution has been further characterised (Found : C, 59·1; H, 4·6; N, 8·3. Calc. for $C_{17}H_{14}O_5N_2$: C, 62·6; H, 4·3; N, 8·6. Calc. for $C_{17}H_{14}O_5N_2.H_2O$: C, 59·3; H, 4·6; N, 8·1%).

Methyl p-(2 : 3-*Dihydroxyprop*-2-*enylideneamino*)*benzoate* (V).—Equimolecular amounts of reductone and methyl *p*-aminobenzoate were allowed to condense under conditions essentially the same as those used by Angier *et al.* (*loc. cit.*) for analogous cases. The *substance* separated from absolute alcohol in yellow rhombs, m. p. 196° after darkening at 180° (Found : C, 60·0; H, 5·3; N, 6·6. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%).

N^4-(2 : 3-*Dihydroxyprop*-2-*enylidene*)*sulphanilamide* (VIII).—Prepared in a similar manner from equimolecular proportions of reductone and sulphanilamide, the *substance* separated from 50% alcohol in tiny yellow needles, m. p. 220° after darkening at 180° (Found, on material dried at 100° in a vacuum : C, 44·2; H, 4·3; N, 11·1. $C_9H_{10}O_4N_2S$ requires C, 44·6; H, 4·1; N, 11·6%).

p-(2 : 3-*Dihydroxyprop*-2-*enylideneamino*)*phenyl Methyl Sulphone* (IX).—Prepared in a similar manner from *p*-methylsulphonylaniline, the *compound* crystallised from 50% alcohol in irregular yellow plates, m. p. 236—238° (Found : C, 50·2; H, 4·6; N, 6·0. $C_{10}H_{11}O_4NS$ requires C, 49·8; H, 4·6; N, 5·8%).

N-p-(2 : 3-*Dihydroxyprop*-2-*enylideneamino*)*benzenesulphonylglycine* (X).—Prepared in a similar manner from sulphanilylglycine (Dewing *et al.*, *J.*, 1942, 242), the *compound* separated from 50% alcohol in yellow needles, m. p. 220° after darkening at 206° (Found : N, 9·2. $C_{11}H_{12}O_6N_2S$ requires N, 9·3%).

N-p-(2 : 3-*Dihydroxyprop*-2-*enylideneamino*)*benzenesulphonylglutamic Acid* (XI).—Reductone (2 g.) was added to a solution of sulphanilyl-L-glutamic acid (6 g.) (Dewing *et al.*, *loc. cit.*) in alcohol (30 c.c.) containing glacial acetic acid (1·2 c.c.). Next day the yellow precipitate (7 g.) was collected. The *substance* separated from alcohol in yellow rectangular plates, m. p. 120—126° (Found : C, 45·7; H, 4·7; N, 7·3. $C_{14}H_{16}O_8N_2S$ requires C, 45·2; H, 4·3; N, 7·5%).

Ethyl Hydrogen N-p-(2 : 3-*Dihydroxyprop*-2-*enylideneamino*)*benzenesulphonylglutamate* (XII).—(i) A solution of acetylsulphanilyl chloride (11·7 g.) in acetone was added to a well-stirred suspension of sodium hydrogen carbonate (4·2 g.) in acetone (30 c.c.) containing diethyl glutamate (10 g.), prepared from the hydrochloride (Chiles and Noyes, *J. Amer. Chem. Soc.*, 1922, **44**, 1802). The mixture was stirred for an hour and kept overnight at room temperature. The acetone solution was then filtered and evaporated, whereupon the product (16 g.) crystallised on treatment with a little alcohol. *Diethyl* N-p-*acetamidobenzenesulphonylglutamate* separated from benzene in felted needles, m. p. 119° (Found : N, 7·6. $C_{17}H_{24}O_7N_2S$ requires N, 7·0%).

(ii) Deacetylation was effected by dissolving the compound (10 g.) in 4N-alcoholic hydrochloric acid (100 c.c.) and allowing the solution to stand at room temperature for 56 hours. Most of the alcohol and the hydrogen chloride were removed in a vacuum at room temperature, and the residue was poured into water and carefully neutralised with ammonia. The oil which separated was recovered by extraction with ethyl acetate but, on isolation, the deacetylated material could not be induced to crystallise. The crude material was therefore dissolved in water (700 c.c.) containing concentrated hydrochloric acid (3·5 c.c.) and treated with reductone (2·5 g.). The mixture was stirred at room temperature for 2 hours and then kept in the refrigerator overnight. The *half-ester* (9·6 g.) separated from absolute alcohol in yellow needles, m. p. 188° [Found : C 48·1, 47·6; H, 4·9 5·4; N, 7·0, 7·1. $C_{16}H_{20}O_8N_2S$ requires C, 48·0; H, 5·0; N, 7·0. $C_{18}H_{24}O_8N_2S$ (diethyl ester) requires C, 50·5; H, 5·6; N, 6·6%].

N^1-2-*Pyrimidyl*-N^4-(2 : 3-*dihydroxyprop*-2-*enylidene*)*sulphanilamide* (XIII).—A solution of reductone (2·5 g.) in water (30 c.c.) was added with stirring to a suspension of finely powdered sulphadiazine (6·3 g.) in water (700 c.c.) containing concentrated hydrochloric acid (3·5 c.c.). Stirring was continued for 2 hours, and the product (8 g.) was collected after the mixture had been kept overnight. The *compound* separated from ethylene glycol in yellow needles, m. p. 260° after darkening at 240° (Found : C, 49·1; H, 4·4; N, 17·7. $C_{13}H_{12}O_4N_4S$ requires C, 48·8; H, 3·8; N, 17·5%).

p-(2-*Amino*-4-*hydroxy*-6-*pteridylmethyl*)*aminobenzoic Acid* (*Pteroic Acid*) (I).—(*a*) A solution of reductone (0·44 g.) and methyl *p*-aminobenzoate (0·75 g.) in alcohol (40 c.c.) was heated under reflux on the water-bath for 15 minutes, and then treated with a suspension of 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (1·3 g.) in water (30 c.c.) containing sodium acetate (0·8 g.; anhydrous). The resulting mixture was heated on the water-bath under nitrogen for 5 hours; a brown solid slowly separated. After cooling, the crude product (1·1 g.) was collected, washed with water, alcohol, and ether, and dried. On hydrolysis by aerated alkali this material afforded an acid having the fluorescence characteristics and absorption spectrum, in alkaline solution, of 2-amino-4-hydroxypteridine-6-carboxylic acid, together with a primary aromatic amine; the same acid was isolated as the product of direct oxidation in alkaline solution with potassium permanganate.

(*b*) The condensation product (V) (2·2 g.), 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (2·5 g.), and sodium acetate (2·5 g., anhydrous) were powdered together and then heated on the water-bath in alcohol (100 c.c.) for 2 hours. The suspension so obtained was filtered and the residue was washed with water, alcohol, and ether, and dried. The crude brown product (2 g.) was dissolved in 0·02N-sodium hydroxide solution (1 l.), and the solution was filtered after adjustment to pH 7. The filtrate was adjusted to pH 3, and the precipitated product was collected. The processes of dissolution and reprecipitation were repeated twice with the addition of decolorising charcoal (0·3 g.), affording a yellow amorphous product (0·22 g.) (Found, on material dried at 160° in a vacuum : C, 53·2; H, 4·1; N, 27·8. Calc. for $C_{14}H_{12}O_3N_6$: C, 53·8; H, 3·8; N, 26·9%).

The absorption spectrum of the substance in 0·1N-sodium hydroxide solution showed maxima at 255 mμ. ($E^{1\%}_{1\,cm.}$ 840), 275 mμ. ($E^{1\%}_{1\,cm.}$ 755), and 365 mμ. ($E^{1\%}_{1\,cm.}$ 290), in good agreement with the values recorded by Wolf *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 2757) and by Waller *et al.* (*ibid.*, 1948, **70**, 20). Cleavage of the substance (80 mg.) in aerated boiling N-sodium hydroxide solution (8 c.c.) for 5 hours afforded an acid (40 mg.), identified by its absorption spectrum and fluorescence characteristics as 2-amino-4-hydroxypteridine-6-carboxylic acid, together with a primary aromatic amine, determined colorimetrically by the Bratton–Marshall method (*J. Biol. Chem.*, 1939, **128**, 537) on an aliquot of the filtrate from the acidified hydrolysis mixture (Found, in terms of *p*-aminobenzoic acid calibration curve : 40 mg. Calc. : 35 mg.).

N^4-(2-*Amino*-4-*hydroxy*-6-*pteridylmethyl*)*sulphanilamide* (XIV).—The condensation product (VIII) (2·5 g.), 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (2·5 g.), and sodium acetate (2·5 g.; anhydrous) were powdered together and heated on the water-bath in alcohol (100 c.c.) for 2 hours. The crude product (3·4 g.) was collected, washed with water, alcohol, and ether, and dried. It was dissolved in hot N-aqueous ammonia at a concentration of 1 mg./c.c., and the hot solution was treated with decolorising charcoal (1 mg. per mg. of crude product) and filtered. The filtrate was acidified at the b. p. with glacial acetic acid, and the hot acidified solution was filtered and cooled, affording a brownish-yellow solid. Dissolution and reprecipitation were repeated twice affording ultimately a yellow microcrystalline *compound* (Found, on material dried at 140° in a vacuum : C, 44·3; H, 3·9; N, 29·1. $C_{13}H_{13}O_3N_7S$ requires C, 45·0; H, 3·7; N, 28·3%).

The absorption spectrum in 0·1N-sodium hydroxide solution showed maxima at 259 mμ. ($E^{1\%}_{1\,cm.}$ 975)

and 365 mμ. ($E^{1\%}_{1\,cm.}$ 275). Hydrolysis of the substance (100 mg.) in aerated N-sodium hydroxide (10 c.c.) afforded 2-amino-4-hydroxypteridine-6-carboxylic acid (60 mg.), identified by its absorption spectrum and fluorescence characteristics, together with a primary aromatic amine, determined colorimetrically as before (Found : 51 mg. Calc. : 49·6 mg.).

p-(2-*Amino*-4-*hydroxy*-6-*pteridylmethyl*)*aminophenyl Methyl Sulphone* (XV).—The condensation product (IX) (4 g.), 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (4 g.), and sodium acetate (4 g., anhydrous) were powdered together and treated as in the preceding case of the sulphanilamide analogue. The crude brown product (3·9 g.) was purified in the manner described in the preceding experiment (1 g. yielding *ca.* 300 mg. of purified material), a yellow *substance* being obtained (Found, on material dried at 150° in a vacuum : C, 48·5; H, 4·1. $C_{14}H_{14}O_3N_6S$ requires C, 48·6; H, 4·0%).

The absorption spectrum in 0·1N-sodium hydroxide showed a maximum at 259 mμ. ($E^{1\%}_{1\,cm.}$ 770) with a " shoulder " at 270 mμ. ($E^{1\%}_{1\,cm.}$ 735) and a maximum at 365 mμ. ($E^{1\%}_{1\,cm.}$ 275). Hydrolysis of the substance (100 mg.) in aerated alkali in the usual way gave 2-amino-4-hydroxypteridine-6-carboxylic acid (55 mg.), identified by its absorption spectrum and fluorescence characteristics, together with a primary aromatic amine, determined colorimetrically (Found : 51 mg. Calc. : 49·6 mg.).

As an alternative method of purification, crystallisation (charcoal) of the crude reaction product (1 g.) from N-sodium hydroxide (50 c.c.) gave yellow needles (0·2 g.) of the sodium salt. Dissolution in very dilute sodium hydroxide and treatment with excess of acetic acid then afforded the same product as above in the form of a light yellow powder (0·14 g.).

N-p-(2-*Amino*-4-*hydroxy*-6-*pteridylmethyl*)*aminobenzenesulphonylglycine* (XVI).—The condensation product (X) (3 g.), 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (2·5 g.), and sodium acetate (2·5 g.) were powdered together and treated in the usual way in alcohol (120 c.c.). After being heated under reflux for 2 hours the suspension was poured into water, the pH was adjusted to 3, and the product (2·4 g.) was collected, washed, and dried. The crude material was purified in the manner described for the sulphanilamide derivative, three treatments affording a light yellow *substance* (Found, after drying at 160° in a vacuum : C, 44·3; H, 4·0; N, 24·0. $C_{15}H_{15}O_5N_7S$ requires C, 44·4; H, 3·7; N, 24·2%).

The absorption spectrum in 0·1N-sodium hydroxide showed maxima at 261 mμ. ($E^{1\%}_{1\,cm.}$ 815) and 365 mμ. ($E^{1\%}_{1\,cm.}$ 235). Cleavage of the substance (75 mg.) in aerated alkali afforded 2-amino-4-hydroxypteridine-6-carboxylic acid (28 mg.), identified by its absorption spectrum and fluorescence characteristics, together with a primary aromatic amine, determined colorimetrically (Found : 27 mg. Calc. : 32 mg.).

N-p-(2-*Amino*-4-*hydroxy*-6-*pteridylmethyl*)*aminobenzenesulphonylglutamic Acid* (XVII).—The condensation product (XII) (8·6 g.), 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (7·4 g.), and sodium acetate (7·4 g.; anhydrous) were powdered together and heated in alcohol (400 c.c.) for 2 hours on the water-bath. About half of the alcohol was distilled off and the residue was treated with water (700 c.c.), the crude product (8·4 g.) being then collected, washed, and dried. The entire crude product was dissolved in water (5 l.) containing N-sodium hydroxide (100 c.c.), on the water-bath. The dark brown solution was adjusted carefully to pH 7, cooled, and filtered. The filtrate was then adjusted to pH 3, and the precipitate was collected. It was then dissolved in N-aqueous ammonia (600 c.c.), and the solution was treated with charcoal (2 g.), filtered, heated to the b. p. and then treated with water (3 l.) containing excess of acetic acid. The flocculent precipitate was collected, and the processes of dissolution in ammonia and reprecipitation were repeated once more, affording a pale yellow *substance* (3 g.) (Found, on material dried at 160° in a vacuum : C, 45·3; H, 4·2; N, 20·2. $C_{18}H_{19}O_7N_7S$ requires C, 45·3; H, 4·0; N, 20·5%).

The absorption spectrum in 0·1N-sodium hydroxide showed maxima at 262 mμ. ($E^{1\%}_{1\,cm.}$ 680) and 365 mμ. ($E^{1\%}_{1\,cm.}$ 200). Hydrolysis of the substance (93 mg.) in aerated alkali afforded 2-amino-4-hydroxypteridine-6-carboxylic acid (30 mg.), identified by its absorption spectrum and fluorescence characteristics, together with a primary aromatic amine, determined colorimetrically (Found : 30 mg. Calc. : 33·6 mg.).

N¹-2-*Pyrimidyl*-N⁴-(2-*amino*-4-*hydroxy*-6-*pteridylmethyl*)*sulphanilamide* (XVIII).—When the conditions used in the preceding condensations were applied to (XIII), the expected reaction did not take place and the following conditions were therefore employed. The condensation product (XIII) (6·4 g.), 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (6·4 g.), and sodium acetate (6·4 g.; anhydrous) were powdered together and heated, with continual stirring under nitrogen, in ethylene glycol (100 c.c.) at 140° for an hour. The dark brown mixture, after cooling, was treated with water, the pH was adjusted to about 3, and the resulting precipitate (8·4 g.) was collected, washed, and dried. The crude product (1·8 g.) was dissolved in hot 2N-aqueous ammonia (900 c.c.) and treated with charcoal (1·8 g.). The filtered solution was heated to the b. p., acidified with acetic acid, filtered hot, and cooled. The solid (0·8 g.), so obtained, was collected and the same process was repeated, affording a light-yellow *substance* (Found, on material dried at 160° in a vacuum : C, 47·2; H, 3·7; N, 29·9. $C_{17}H_{15}O_3N_9S$ requires C, 48·0; H, 3·5; N, 29·7%). The absorption spectrum in 0·1N-sodium hydroxide showed maxima at 259 mμ. ($E^{1\%}_{1\,cm.}$ 870) and 367 mμ. ($E^{1\%}_{1\,cm.}$ 220). Hydrolysis of the substance (92 mg.) in aerated alkali afforded 2-amino-4-hydroxypteridine-6-carboxylic acid (40 mg.), identified in the usual way, together with a primary aromatic amine, determined colorimetrically (Found : 36 mg. Calc. : 37·6 mg.).

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427. *Septum Hydrogenation.*

By A. R. Ubbelohde.

Hydrogenation of molecules can be carried out by the uptake of hydrogen discharged electrolytically and diffusing through a metal septum. Thermodynamics indicates that septum hydrogenation should provide a possible alternative to catalytic hydrogenation at high pressures. Practical limitations to this possibility throw new light on the mechanism of catalytic hydrogenation, and on the chemical state of hydrogen dissolved in metals.

Possibilities of Septum Hydrogenation.—When hydrogen ions are discharged at certain metal electrodes, such as iron, platinum, or palladium, the hydrogen is found to diffuse through the metal. Various lines of evidence indicate that diffusion occurs in the form of atoms. If the electrode forms a septum, for example, a cylinder or plate separating two media, discharge of ions on the one side can be followed by the appearance of gaseous hydrogen on the other side of the septum. The pressure of gas built up depends on such factors as the current density, and the solubility and rate of diffusion of hydrogen atoms through the metal.

It is noteworthy that comparatively very high pressures of gas can be built up by means of relatively small current densities. These high pressures appear to be responsible for certain characteristic cracks, which are formed when the gas is evolved at minute fissures within the metal. A quantitative relationship established empirically by Borelius and Lindblom for iron septa (*Ann. Physik*, 1927, **82**, 201) gives

$$p = 17{,}000\,I \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where p is the pressure in atmospheres on one side of the septum, corresponding with a current density I amp./sq. cm. of hydrogen ions discharged on the other side of the septum. Values of p up to 16 atm. have been reported by Borelius and Lindblom, who do not however discuss at what limiting pressures this relationship would break down.

This supply of hydrogen to the septum face from within the metal is of considerable interest for a number of physicochemical investigations. Two related problems which are discussed in the present paper are: (i) How far septum hydrogenation might be used to replace hydrogenation by gaseous hydrogen at high pressures. (ii) How far the catalytic activity of hydrogen arriving at the septum face from within the metal differs from the catalytic activity of hydrogen adsorbed on the metal surface from the gas phase.

Reduction Potentials in Septum Hydrogenation.—Owing to their technological importance, the pressures of hydrogen set up on the gas face of metal septa, particularly of iron, during electrolysis have been investigated by a number of authors. Other transitional metals have also been studied (Borelius and Lindblom, *loc. cit.*; Aten and Zieren, *Rec. Trav. chim.*, 1930, **49**, 641; Morris, *J. Soc. Chem. Ind.*, 1935, **54**, 7T; Barrer, *Trans. Faraday Soc.*, 1940, **36**, 1935).

The magnitudes in the empirical equation (1) may be correlated with Tafel's equation which relates the over-voltage E_S for discharge of hydrogen ion with the current density I:

$$E_S = a + b \log I \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

A general argument about the thermodynamics of irreversible processes may be developed without going into all the complexities which arise in connection with the discharge of hydrogen at electrodes (cf. Bockris, *Chem. Reviews*, 1948, **3**, 526). Attention may be fixed on the layer of freshly discharged hydrogen at the electrolyte face of the septum. This layer supplies both the hydrogen in the gas bubbles which are evolved on the electrolyte side of the septum, and the hydrogen which diffuses through to the gas face of the septum. On account of the irreversibility of discharge of gas bubbles, there is at most electrodes an "overpotential" between this freshly discharged hydrogen and the hydrogen in the gas bubbles. The small effect of surface tension on gas pressure in the bubbles being neglected, once the hydrogen comes off in a bubble it is at 1 atm. pressure.

Whatever the physicochemical origins of the irreversibility on the electrolyte side of the septum, the difference $\Delta\mu$ in thermodynamic potential between the hydrogen freshly discharged at the septum face and hydrogen at 1 atm. pressure in the gas bubbles cannot exceed the maximum free energy which could be obtained from a potential difference E_S if utilised in a reversible process, *i.e.*,

$$FE_S \geqslant \Delta\mu \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where E_S is in volts and $F = 96{,}494$ coulombs. Again, on the gas side of the septum, the maximum pressure p of hydrogen (in atm.) cannot exceed the value which would give the same

thermodynamic potential to the hydrogen on both sides of the septum. It may be substantially smaller, if irreversible processes are involved to an important extent in the transfer of hydrogen through the septum, *i.e.*,

$$\Delta\mu \geqslant RT \ln p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Combination with (3) gives

$$E_s \geqslant [RT/F] \ln p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Insertion of the empirical relation (1) for iron septa gives

$$E_s \geqslant RT[\ln 17{,}000 + \ln I]/F$$

and introduction of numerical constants at 25° leads to

$$E_s \geqslant 0{\cdot}25 + 0{\cdot}06 \log I \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Although the constants in Tafel's equation do not appear to be free from controversy in the case of iron (Bockris, *loc. cit.*, p. 537), the numerical values in equation (6) are in line with values for other transitional metals.

If this correlation between Tafel's equation and the septum equation (1) is accepted, important conclusions for the possibilities of septum hydrogenation are:

(*a*) Very high hydrogenation pressures should be equivalent to quite accessible current densities, especially if the irreversible processes in transferring hydrogen through the septum do not lead to the dissipation of much of the free energy of the hydrogen.

(*b*) The maximum free energy of the hydrogen available is determined by the overvoltage which can be realised at the electrolyte face of the septum. For example, experiments (Bockris, *loc. cit.*, p. 546) indicate that poisoning of the iron face by arsenic or mercury can substantially increase this overpotential. Such poisoning should correspondingly raise the potential of hydrogen available. Support for this conclusion is obtained from the fact that the diffusion pressures of hydrogen through iron septa are *increased* on poisoning the electrolyte face with mercury or arsenic (Aten and Zieren, *loc. cit.*). Limitation to the possible usefulness of septum hydrogenation arise from the fact that potential barriers may hinder the entry of hydrogen into the metal, and also the exit of hydrogen from the metal. The significance of these exit barriers is further discussed below. A further limitation is that, except at high temperatures or for very thin septa, the rate of hydrogen transfer is rather slow.

Experimental.

Experiments on Septum Hydrogenation.—Attempts to measure the electrode potential of hydrogen diffusing through a metal septum have been reported by various authors (cf. Bodenstein, *Z. Elektrochem.*, 1922, **28**, 517; Aten and Zieren, *loc. cit.*; Bockris, *loc. cit.*, p. 541).

As is illustrated below, more detailed information about septum hydrogenation can be obtained by investigating specific hydrogenation reactions. The experiments were carried out to obtain a preliminary survey of the practical possibilities of septum hydrogenation, for example, as a means of circumventing the need for pressure hydrogenation of certain organic substances which are available only in small quantities. Various forms of apparatus were tested.

Fig. 1 illustrates apparatus with which many experiments were made. Two condensers were used in view of the fact that hydrogenation was normally investigated at the boiling point of the solutions, in order to keep the solutions stirred, and to secure maximum diffusion rate for the hydrogen. Various authors have established the dependence of the diffusion coefficient of hydrogen D through a metal

$$D = (k/d) \exp[-E/RT]$$

where k is a constant characteristic of the metal, d is the thickness, and E is the activation energy for diffusion. This makes it desirable to accelerate diffusion of hydrogen by working at the highest possible temperature.

The electrolyte vessel, containing either 10% sulphuric acid or 10% sodium hydroxide, and the hydrogenation vessel were heated by means of nichrome wire carrying a current. They were separated by a septum whose construction is detailed in Fig. 1*a*. It consisted of a circular plate of copper 0·1" thick. This plate had a central oblong aperture approx. 4 × 5 cm., in which a thin metal sheet, the "septum," was hard soldered. The whole surface except the two faces of the septum was thickly plated with silver and then gold to protect it from corrosion.

The metal sheets available for use as septa were: "Shim" steel 0·04 mm. thick, palladium 0·02 mm. thick, and platinum 0·01 mm. thick.

Gaskets of polythene 0·2 cm. thick gave satisfactory resistance to leakage, if the screws were tightened whilst the system was hot. Polythene was considered to be fairly unobjectionable on chemical grounds.

A more elegant apparatus for septum hydrogenation avoided the need for any gaskets, by carrying out the electrolysis in a nickel test-tube about 1·5 cm. in diameter and 15 cm. long which was immersed in the solution undergoing reduction. The top of the test-tube fitted into a condenser to permit the

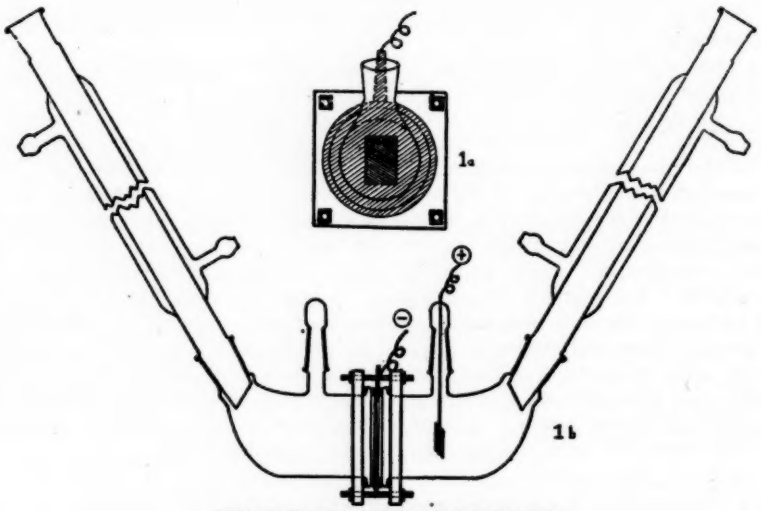
use of boiling electrolyte. Part of the walls of the test-tube was replaced by platinum or palladium septa, and the remainder was heavily silver-plated and coated with bakelite varnish to prevent attack of the nickel.

On the electrolyte side of this " test-tube " the metal was made cathodic, and a central platinum anode completed the circuit. By this means the septa formed windows for letting reducing hydrogen into the solutions under investigation. Technical difficulties arose in the construction of such test-tubes, which had a rather short life. On account of the limited supply of metal foils available, the bulk of the experiments were carried out with the simpler septa with sealing gaskets, described above.

Even when used in plate form, both the iron and the palladium septa had comparatively short lives owing to recrystallisation and chemical action, leading to tearing. The platinum septum was much more durable.

To explore the kind of behaviour to be expected, three main types of reduction were followed. The progress of hydrogenation was ascertained in (i) by observing colour changes and in (ii) and (iii) by withdrawing aliquot portions of solution from the hydrogenation side of the septum, and carrying out appropriate analyses.

FIG. 1.



APPARATUS FOR SEPTUM HYDROGENATION

(i) *Reduction of aqueous solutions of organic molecules.* Approximately M/100-aqueous solutions were used of methylene-blue, of the zinc chloride complex with malachite-green, and of neutral and acid benzoquinone. In no case was complete decoloration achieved even on prolonged reduction for several hours, using a current density of approx. 1 amp./sq. cm. and a palladium septum. Benzoquinone solutions in water or aqueous alcohol rapidly developed a deep brown quinone–quinol colour, and appeared to reach a steady state in about 3—4 hours. A less highly coloured steady state was reached with the acid solutions. This might be expected if the reduction reaches an end-point determined by the thermodynamic potential of the hydrogen available at the septum face.

(ii) *Reduction of organic molecules in organic solvents.* (*a*) Oleic acid gave evidence of some reduction at 100°, a platinum septum being used with a current density of 0·3 amp./sq. cm., and the unsaturation being determined with Wijs's reagent. However, a complicated side reaction also took place, which led to the formation of dark by-products and made it difficult to analyse the amount of stearic acid formed.

(*b*) Nitrobenzene in glacial acetic acid at about 118° was reduced through a platinum septum. Unchanged nitrobenzene at the end of an experiment was estimated by pouring into water. The observed reduction (calculated as aniline) corresponded with a rate of transfer of approximately 6×10^{-6} g.-atom of hydrogen per sq. cm./min. at 118° for a current density of 0·3 amp./sq. cm.

(iii) *Reduction of inorganic compounds in aqueous solution.* (*a*) The reduction of iodine dissolved in aqueous potassium iodide could readily be followed by titration with sodium thiosulphate. Rapid diffusion of hydrogen was observed in the case of iron septa, but since the metal also appeared to be attacked by the iodine no quantitative data could be obtained on the rate of transfer of reducing hydrogen through the septum. With a palladium septum, the reduction rate corresponded to a transfer of approximately 4×10^{-6} g.-atom of hydrogen per min. per sq. cm. for a current density of 0·9 amp./sq. cm. at about 30°. These experiments were carried out with an " immersion test-tube " type of apparatus.

(*b*) Reduction in sulphuric acid solution, $Fe^{\cdot\cdot\cdot} \longrightarrow Fe^{\cdot\cdot}$, with a platinum septum was followed under various conditions, by titrating ferrous ion produced with potassium permanganate. The maximum rate of transfer of hydrogen observed was when the septum on the electrolysis side was first activated. For this purpose it was made anodic for about 10 minutes, at a current density of 1 amp./sq. cm., before being made cathodic.

The rates of transfer ranged from approximately 2×10^{-7} to 5×10^{-7} g.-atom of hydrogen per min. per sq. cm. at 100°, for a current density of 0·37 amp./sq. cm.

Discussion.

(i) *Scope of Septum Hydrogenation.—End-point of reduction.* Although the experiments were only exploratory, they serve to illustrate the fact that septum hydrogenation can be carried out to a satisfactory end-point only for reactions involving moderate reduction potentials. The reason for this became apparent in the course of the work. As is explained above (equation 6), the maximum reduction potential available in this type of hydrogenation has as upper limit the overpotential for evolution of hydrogen at the electrolysis side of the septum.

Rate of reduction. The rate of septum hydrogenation is rather slow since it is limited by the rate of diffusion of hydrogen through the septum. Higher temperatures of reduction than those used in the present work could be realised without too much difficulty, particularly with the test-tube apparatus. It should also be possible to devise alloys more permeable to hydrogen than pure platinum and not so liable to cracking as pure palladium.

Efficiency of reduction. An important consideration for the fundamental theory of catalysis is the efficiency of septum hydrogenation. One definition of this efficiency is the ratio

$$r_1 = \frac{\text{g.-atoms of } H_2 \text{ effecting reduction in unit time}}{\text{g.-atoms of } H_2 \text{ arriving at the septum face in unit time}} \quad . \quad . \quad . \quad . \quad (7)$$

In order to calculate this efficiency, a knowledge is required of the rate of arrival of hydrogen atoms at the inner face of the exit side of the septum. A *lower* limit to this rate can be obtained experimentally from measurements of the rate of evolution of gaseous hydrogen when the exit side of the septum is exposed to vacuum. If no activation process were required for the reaction

$$\text{H (dissolved in metal)} \longrightarrow H_2 \text{ gas (exit side of septum)} \quad . \quad . \quad . \quad . \quad . \quad (8)$$

the rate of gas evolution into a vacuum should be identical with the rate of arrival at the inner face of the septum. On the other hand, if there is a potential barrier, this barrier may be substantially lower for the combination of hydrogen atoms with molecules adsorbed on the exit side of the septum in a process such as

$$\text{H (dissolved in metal)} \longrightarrow \text{H–M (combined with molecules adsorbed on septum face)} \quad . \quad . \quad (9)$$

than for the evolution of hydrogen molecules. What this would imply experimentally is that the rate of transfer of hydrogen atoms effecting reduction according to (9) may be many times as large as the rate of transfer of atoms leading to evolution of gaseous hydrogen according to (8).

Obviously, such a possibility is of great interest in elucidating the mechanism of catalytic hydrogenation. Although data are not yet available for estimating the efficiency according to (7), experimental data permit the calculation of the related ratio

$$r_2 = \frac{\text{g.-atoms of } H_2 \text{ effecting reduction in unit time}}{\text{g.-atoms of } H_2 \text{ evolved as } H_2 \text{ under comparable conditions}}$$

Fully conclusive evidence can only be obtained by experiments on the same septum, in which the rate of evolution of gaseous hydrogen and the rate of reduction of various molecules can be directly compared. Such experiments are not, of course, restricted to reduction in liquid systems. It has not yet been possible to carry out such parallel experiments on the same septum. Comparisons may, however, be made with experiments by other authors, as follows.

Palladium. Data are given by Barrer (*Trans. Faraday Soc.*, 1940, **36**, 1235) on the permeability P, measured in c.c. of gas (at N.T.P.) transferred per sq. cm. per sec. through a plate 1 mm. thick for a current density of 1 amp./sq. cm. A range of values is observed according to the activity of the metal. The highest permeability observed by Barrer, when recalculated for a current density of 0·9 amp. per sq. cm., would correspond to $9{\cdot}3 \times 10^{-6}$ g.-atom of hydrogen per sq. cm. per min. for reaction (8) as compared with 4×10^{-6} for reaction (9) in the present experiments, for the reduction of iodine in potassium iodide. So far as this evidence goes, there are thus no grounds for expecting large differences between processes (8) and (9) for palladium septa, at any rate for the reduction of iodine. Further evidence is however desirable in view of the interest of the problem.

Platinum. No direct measurements appear to be available on the rate of evolution of gaseous hydrogen from the exit side of a platinum septum when the entry side is charged electrolytically. It seems likely that this rate is small.

The ratio of permeation velocities of gaseous hydrogen through palladium and platinum can be calculated from data quoted by Smithells and Ransley (*Proc. Roy. Soc.*, 1935, **150**, 172). At 373° this ratio is

$$\mathrm{Pd/Pt} = \frac{1{\cdot}18 \exp (9000/373)}{1{\cdot}41 \exp (2100/373)} = 8{\cdot}4 \times 10^{7} \text{ for reaction (8)}$$

If there were no catalytic effects at the septum face, the ratio of permeabilities to hydrogen determined according to reaction (8) should be the same as the ratio of the g.-atoms of hydrogen available for reduction under comparable conditions according to reaction (9). Although no exact ratio can yet be established, owing to the exhaustion of supply of a particular batch of palladium foil, if the ratio of reducing hydrogen atoms in (iii) is compared, differences in the reactions studied and in the current densities being neglected, this gives

$$\mathrm{Pd/Pt} = 4 \times 10^{-6}/5 \times 10^{-7}$$

a factor of about 8. Thus there appears to be a marked difference between the two septa for reaction (8) and reaction (9).

Various explanations of this difference can be suggested. The most likely seems to be that the exit of hydrogen atoms for a catalytic reduction (9) involves a much smaller barrier at the platinum septum face than the exit of hydrogen as molecules, according to (8). This contrasts with palladium, for which any barriers appear to be about the same for the two processes. Further work is needed to substantiate and develop the implications of this interesting difference.

Availability of the Hydrogen from within a Septum.—Experiments by Bodenstein (*loc. cit.*) indicate that the *atoms* within the metal of a palladium septum are not available for starting various chain reactions such as $H_2 + Cl_2$ or $H_2 + O_2$ or even for reacting with bromine. It is useful to consider briefly two alternative models for representing the processes under discussion since these orient further lines of investigation.

(a) *The interstitial proton gas/potential barrier model for septum hydrogenation.* A generalised description of the state of hydrogen atoms dissolved in a metal such as palladium or platinum is to regard the hydrogen as a proton gas, partly dissociated from its accompanying electrons, and occupying the interstitial space between the atoms of the metal. Considerations about the expansion pressures of such a gas (Ubbelohde, *Proc. Roy. Soc.*, 1937, **159**, *A*, 295; and in publication) do not wholly favour this extremely generalised description. It does, however, lend itself to the conventional formulation of potential barriers for the extraction of protons from the interior to the surface of the metal forming the septum, analogous to the barriers for extracting electrons. On this model, work is required to remove the proton and the electron to the surface. Once these have reached the surface they form hydrogen atoms which will exhibit a finite rate of recombination to molecules dependent on a number of surface factors. Combination with molecules on the surface can also occur in favourable circumstances.

(b) *The "pseudometallic hydride" model.* According to this model, specific metal atoms A form ordinary covalent bonds with H, and each "pseudo-atom" (A–H) behaves like the next atom to the right in the same row of the Periodic System (Ubbelohde, in publication). Usually these (A–H) pseudo-atoms are still capable of acting as metals, *i.e.*, they have vacant electron orbits and can form shared covalent bonds in close-packed systems of atoms (cf. Pauling's theories of metallic binding).

By way of illustration, on this view, $PdH_{0{\cdot}6}$ should be represented as $Pd_2(PdH)_3$, which should be similar in many ways to the alloy Pd_2Ag_3. In particular, any (PdH) pseudo-atom forms the same number of covalent linkages as any Ag atom, provided it is wholly surrounded by other atoms of Pd or (PdH). The composition of an alloy of particular crystal structure can usually assume a range of values.

At the surface, if the A–H bond lies within the lattice pointing downwards, the régime is analogous to that within the metal. If, however, an A atom is partly detached from the remaining atoms in the lattice, or if the A–H bond is directed outwards from the surface, it will no longer be stabilised by metallic linkages. Transfers of hydrogen atoms to other molecules can be facilitated from these partly detached (A–H) atoms.

On this model, catalytic hydrogenation at a septum can be represented by a series of chemical bond transfers such as

$$\text{(A–H) interior} + \text{A (surface)} \longrightarrow \text{(A–H) surface, partly detached} + \text{A (interior)}$$

$$\text{(A–H) surface, partly detached} \longrightarrow \begin{cases} \longrightarrow H_2 \text{ gas} + \text{A (surface)} \\ \longrightarrow \text{H–M (combination with adsorbed molecules)} + \text{A (surface)} \end{cases}$$

Although the two models are merely to be regarded as alternative descriptions of the same process, the " pseudo-atomic " hydride model lends itself more readily to the consideration of specific chemical bond transfers such as may be influenced by local atomic impurities, and such as are operative in catalytic hydrogenation at the septum face.

QUEEN'S UNIVERSITY, BELFAST. [*Received, March 29th*, 1949.]

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428. *Aromatic Hydrocarbons. Part LI. The Synthesis of Dinaphthopyrenes.**

By E. CLAR.

Pyrene was condensed with two molecules of phthalic anhydride, and the two isomeric dicarboxylic acids were separated. Ring-closure gave two phthaloylpyrenes, and thence, by reduction, hydrocarbons which are regarded as dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-8 : 9)-pyrene and dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-9 : 10)pyrene, respectively, by analogy with the corresponding dibenzpyrenes. Oxidation of the hydrocarbons yielded the corresponding dinaphthopyrenequinones.

PYRENE condenses with two molecules of phthalic anhydride in a melt of sodium chloride–aluminium chloride at 150—160° with the formation of a diphthaloylpyrene in small yields (Vollmann, Becker, Corell, and Streeck, *Annalen*, 1937, **531**, 128). It has now been found that two isomeric diphthaloylpyrenes are formed in this condensation, and that they can be obtained pure and in good yield if the reaction is carried out in two stages. Pyrene was condensed with an excess of phthalic anhydride and aluminium chloride in tetrachloroethane at 70—80° and the dicarboxylic acids (I) and (II) were separated by means of the more sparingly soluble sodium salt of the (II). Ring-closure of these acids with boiling benzoyl chloride and a trace of sulphuric acid gave the orange diquinones (III) and (IV). Of these, only (IV) dissolved (with a green colour) in sulphuric acid, (III) being insoluble, and this difference provided another method of separating the two condensation products. Reduction of the diquinones was carried out by means of the zinc-dust melt (Clar, *Ber.*, 1939, **72**, 1645) or, better, with pyridine, zinc dust, and acetic acid (Clar, *Chem. Ber.*, 1948, **81**, 68). Dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-8 : 9)-pyrene (V) is a blue hydrocarbon which reacts easily, like a higher acene, with maleic anhydride in solution. However, the oxidation with selenium dioxide in boiling nitrobenzene did not yield a *p*-quinone, but gave the red dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-8 : 9)pyrene-5 : 10-quinone (VII). The yellow dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-9 : 10)pyrene (VI) reacted considerably more slowly with maleic anhydride than did (V), and by taking advantage of this (V) could be removed from a mixture with (VI). Oxidation of (VI) gave dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-9 : 10)pyrene-5 : 8-quinone (VIII), which is a violet vat dye. These oxidation results show that the two hydrocarbons belong to the pyrene rather than to the acene series.

Fig. 1 shows the absorption spectra of the centro-symmetric (V), 3 : 4-8 : 9-dibenzpyrene, and pyrene. The square root of the wave-length of the first band of the first intense group of bands increases by the same amount ($\sim 9\sqrt{\text{A.}}$) with each increase in the number of rings, as required by the anellation principle (Clar, " Aromatische Kohlenwasserstoffe," Berlin, 1941, p. 20). The shift towards the red amounts to half of this value ($\sim 4{\cdot}5\sqrt{\text{A.}}$) in the plane-symmetric series (VI), 3 : 4-9 : 10-dibenzpyrene, and pyrene. The theoretical implications of this will be discussed elsewhere. Comparison of these absorption spectra shows clearly that the structures assigned to the hydrocarbons are correct. Further evidence is provided by the pyrenequinones : the plane-symmetric quinones are deeper coloured than the centro-symmetric

* Part L, *Nature*, 1949, **163**, 921.

quinones; thus the pyrene- and dibenzpyrene-quinones are yellow and red, respectively, the dinaphtho-pyrenequinones (VII) and (VIII) are red and violet, respectively.

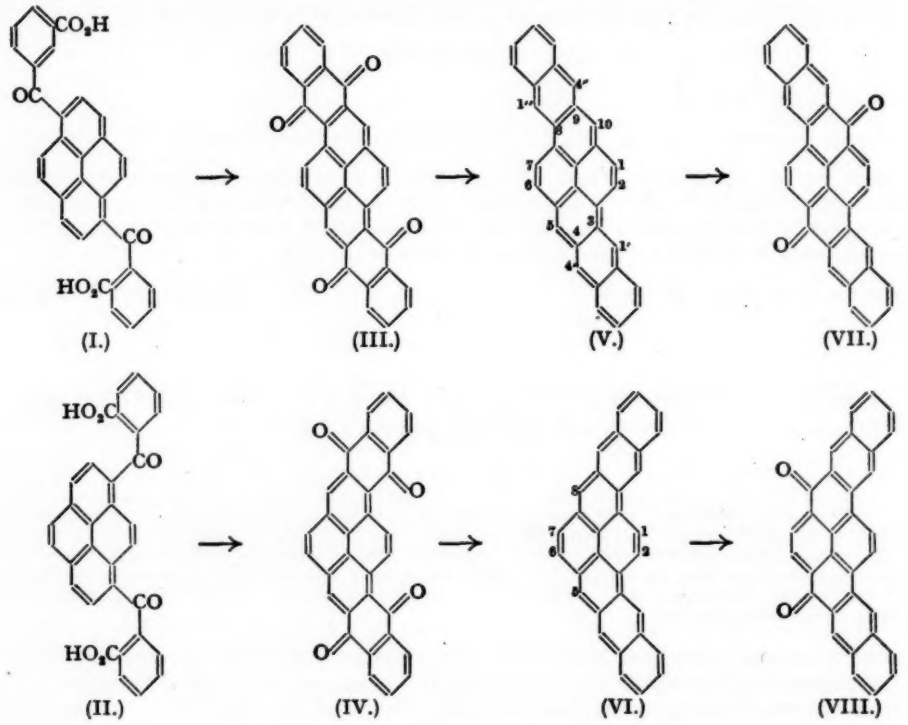
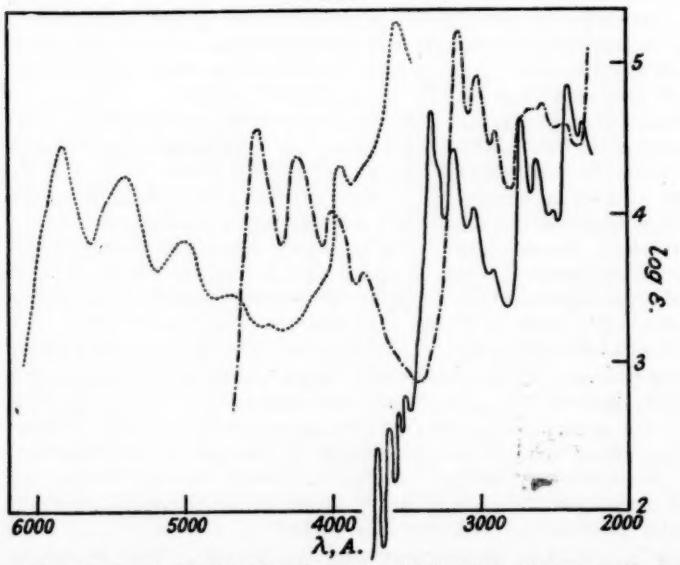


FIG. 1.

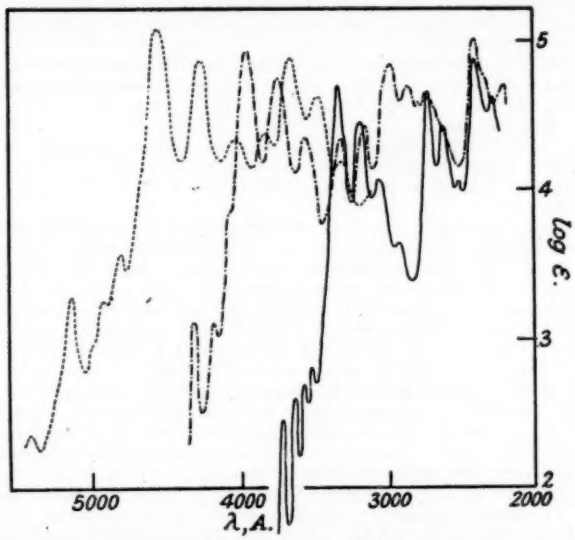


. . . . . *Absorption spectrum of dinaphtho*(2′ : 3′-3 : 4)(2″ : 3″-8 : 9)*pyrene* (*V*) *in* 1-*methylnaphthalene. Band maxima* (*in* A.): 5820, 5390, 4990, 4660, 4400; 3930; 3530.

— · — · — *Absorption spectrum of* 3 : 4-8 : 9-*dibenzpyrene. Band maxima* (*in* A.): 4510, 4240, 4010, 3790; 3135; 3010, 2900 *in benzene*, 2640, 2560, 2420 *in alcohol.*

——— *Absorption spectrum of pyrene in alcohol. Band maxima* (*in* A.): 3715, 3620, 3560, 3515; 3335, 3180, 3050, 2920; 2720, 2615, 2510; 2410; 2305.

FIG. 2.



. . . . . *Absorption spectrum of dinaphtho*(2′ : 3′-3 : 4)(2″ : 3″-9 : 10)*pyrene* (*VI*) *in trichlorobenzene. Band maxima* (*in* A.) : 5450; 5150, 5940, 4820; 4560, 4270, 4030; 3820; 3655, 3490, 3310.

— · — · — *Absorption spectrum of* 3 : 4-9 : 10-*dibenzpyrene. Band maxima* (*in* A.) : 4330, 4190, 4080; 3970, 3750, 3565; 3320, 3170, 2970, 2850 *in benzene*, 2720; 2420, 2220 *in alcohol*.

———— *Absorption spectrum of pyrene as in Fig.* 1.

EXPERIMENTAL.

3 : 10-*Di*-(o-*carboxybenzoyl*)*pyrene* (II).—Pyrene (40 g.) and phthalic anhydride (70 g.) were melted together, and tetrachloroethane (130 c.c.) was poured into the hot liquid. Powdered aluminium chloride (130 g.) was gradually added at 50°, and the mixture was heated for one hour at 70°. After decomposition with dilute hydrochloric acid in the usual way, the tetrachloroethane was removed by steam-distillation, and the residue washed with water and dissolved in dilute sodium hydroxide solution. The hot solution was made just acid with acetic acid in order to separate impurities. The dicarboxylic acid (90 g.) was then precipitated with hydrochloric acid, powdered, and treated with 200 c.c. of boiling acetic acid. After the mixture had cooled, the crystals (40 g.) were collected and washed with ether. Repeated recrystallisation from dilute aqueous sodium hydroxide gave yellow needles (11 g.) of the sodium salt of 3 : 10-*di*-(o-*carboxy*)*benzoylpyrene* (II). The free acid obtained from it by acidification crystallised from 1-methylnaphthalene in yellow needles, m. p. 325° (decomp.), which dissolved in sulphuric acid to give a red solution which afterwards turned blue (Found : C, 77·6; H, 3·9. $C_{32}H_{18}O_6$ requires C, 77·1; H, 3·6%). 3 : 8-*Di*-(o-*carboxybenzoyl*)*pyrene* (I) was obtained by acidification of the alkaline mother-liquors from the recrystallisation of the salt of (II). Recrystallisation from nitrobenzene yielded pale yellow crystals, m. p. 305—310° (decomp.), which dissolved in sulphuric acid giving a violet solution which turned green on heating (Found : C, 76·0; H, 3·8. $C_{32}H_{18}O_6$ requires C, 77·1; H, 3·6%). This purification does not ensure that the product is free from its isomer, which sometimes can be traced in the subsequent condensation.

3 : 4-8 : 9-*Diphthaloylpyrene* (III).—The acid (I) (5 g.), benzoyl chloride (15 g.), and two drops of concentrated sulphuric acid in nitrobenzene (150 c.c.) were boiled for ½ hour. A thick mass of orange needles which was precipitated from the hot liquid was filtered off at 100° and washed with nitrobenzene and ether (yield, 4·3 g.). Recrystallisation from nitrobenzene gave orange needles, which sintered at 450° (evacuated capillary; uncorr.) and charred, without melting, at higher temperatures (Found : C, 83·0; H, 3·3. $C_{32}H_{14}O_4$ requires C, 83·1; H, 3·1%). The pure *diquinone* is not soluble in cold concentrated sulphuric acid. Occasionally green solution indicates the presence of the isomeric diquinone which can be removed by filtering through a porous filter-plate. 3 : 4-9 : 10-*Diphthaloylpyrene* (IV), prepared in the same way from 3 : 10-di-(o-carboxybenzoyl)pyrene (II), formed orange needles, m. p. 450—455° (evacuated capillary; uncorr.), which dissolve in concentrated sulphuric acid with a pure green colour (Found : C, 83·2; H, 3·6%). Both diquinones gave a brownish-red vat in alkaline sodium hydrosulphite (dithionite).

Reduction of the Diquinones.—(a) *By the zinc dust melt.* The diquinone (5 g.) and zinc dust (10 g.) were finely powdered together, and sodium chloride (7 g.) and moist zinc chloride (25 g.) were added. The mixture was melted, stirred, and heated to 300° within about 15 minutes. The cold melt was dissolved in hydrochloric acid. The excess of zinc dust was thus removed, and the carefully washed residue was sublimed at 1 mm. in a current of carbon dioxide. The sublimate was recrystallised from 1-methylnaphthalene.

(b) *By zinc dust, pyridine, and acetic acid.* Acetic acid (80%; 50 c.c.) was added drop by drop

to a boiling suspension of diquinone (5 g.), zinc dust (13 g.), and pyridine (120 c.c.) during 5 hours. The solution, which was at first red, became gradually pale-orange and was decanted from the zinc dust and poured into water. Sublimation of the washed precipitate or recrystallisation from 1-methylnaphthalene yielded the hydrocarbon.

Dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-8 : 9)*pyrene* (V) formed beautiful blue leaflets, m. p. 460° (evacuated capillary; uncorr.), which gave a brownish-yellow solution in concentrated sulphuric acid (Found: C, 95·6; H, 4·9. $C_{32}H_{18}$ requires C, 95·5; H, 4·5%). Its solutions in xylene or 1-methylnaphthalene show a strong orange fluorescence.

Dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-9 : 10)*pyrene* (VI) formed yellow leaflets, m. p. 420° (evacuated capillary; uncorr.), which dissolved in concentrated sulphuric acid to give a brown solution, which afterwards turned green and then blue (Found: C, 95·4; H, 4·7%). The solution in xylene showed a strong green fluorescence.

Mixtures of the hydrocarbons (V) and (VI) can be separated by adding small portions of maleic anhydride to the boiling solution in nitrobenzene or 1-methylnaphthalene until the visible spectrum of (V) has almost disappeared; (VI) then crystallises unchanged. Since the blue (V) is considerably less soluble than (VI), it can be obtained from the mixture with (VI) by simple fractional crystallisation.

Oxidation of the Hydrocarbons.—The hydrocarbon (1·5 g.) and selenium dioxide in nitrobenzene (150 c.c.) was boiled for ½ hour. After the mixture had cooled, the precipitate was filtered off, washed with nitrobenzene, ether, water, and alcohol, and sublimed at 1 mm. in a current of carbon dioxide. The selenium sublimed first and could be easily separated from the quinone.

Dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-8 : 9)*pyrene*-5 : 10-*quinone* (VII) sublimed in dark-reddish-brown, silky needles, m. p. 479° (decomp.) (evacuated capillary; uncorr.) (Found: C, 88·7; H, 3·7. $C_{32}H_{16}O_2$ requires C, 88·8; H, 3·7%). The solution in concentrated sulphuric acid was pure green, and gave a red precipitate when poured into water. The vat in alkaline hydrosulphite is brownish-olive-red in a thin layer and yields the deep red quinone on oxidation with air.

Dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-9 : 10)*pyrene*-5 : 8-*quinone* (VIII) sublimed in dark violet needles, m. p. 460° (decomp.) (evacuated capillary; uncorr.), which gave a brown solution in concentrated sulphuric acid (Found: C, 88·8; H, 4·1%). A violet vat is formed with alkaline sodium hydrosulphite, from which the violet quinone is precipitated by air.

This work was carried out during the tenure of an I.C.I. Research Fellowship, for which I express my indebtedness.

UNIVERSITY OF GLASGOW. [*Received, December 13th*, 1948.]

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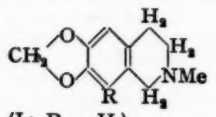
429. *Reduction of Cotarnine and Certain Derivatives thereof.*

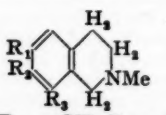
By DAVID B. CLAYSON.

Reduction of hydrocotarnine with sodium and *iso*amyl alcohol in xylene gives hydrohydrastinine, whereas with sodium and liquid ammonia 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (III) is produced. Cotarnine with sodium and liquid ammonia, to which ammonium chloride or sodium hydroxide has been added, gives (III) or 1 : 6-dihydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline, respectively. Some 2 : 2-dimethyltetrahydro*iso*quinolinium iodides were reduced by sodium and liquid ammonia to the corrresponding dimethyl-2-*o*-tolylethylamines.

THE production of hydrohydrastinine (I) from hydrocotarnine (II) was first carried out by Pyman and Remfry (*J.*, 1912, 1595) who also obtained small quantities of the related phenolic bases (III), (IV), (V), and (VI). Reduction by sodium and alcohol was also applied by Kondo and Nagasato (*J. Pharm. Soc. Japan*, 1924, **507**, 326) to cotarnine itself with the formation of hydrocotarnine, hydrohydrastinine, and 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro-*iso*quinoline (III). The use of inert solvents in reductions of this nature has been shown to lead to increased yields of the final product (Rowe, *J. Soc. Chem. Ind.*, 1920, **39**, 241T).



(I; R = H.)
(II; R = OMe.)



(III; R_1 = OH, R_2 = H, R_3 = OMe.)
(IV; R_1 = H, R_2 = OH, R_3 = OMe.)
(V; R_1 = R_2 = H, R_3 = OH.)
(VI; R_1 = OH, R_2 = R_3 = H.)

The hydrocotarnine used in the present work was obtained by catalytic reduction of cotarnine hydrochloride with hydrogen and Adams's catalyst, which was found to be more convenient than those previously described (Pyman and Remfry, *loc. cit.*; Beckett and Wright, *J.*, 1875, **28**, 577; Bandow and Wolffenstein, *Ber.*, 1898, **31**, 1577).

The results of various reductions of hydrocotarnine by sodium, an alcohol, and an inert

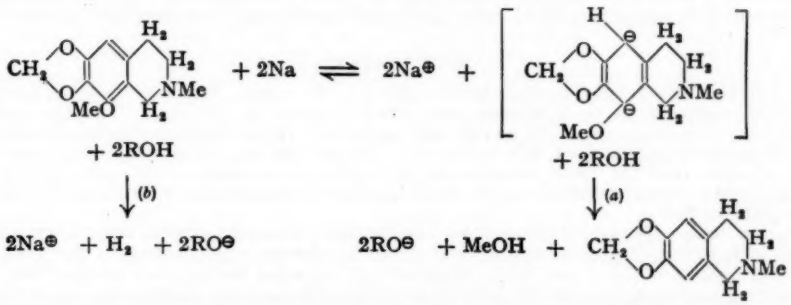
solvent are summarised in the table. The nature of the solvent and of the alcohol, as well as the quantity of sodium used, were all of critical importance to the final yield, the best results being obtained with *iso*amyl alcohol, xylene, and six atoms of sodium for each molecule of hydrocotarnine. In experiments on a larger scale the yields were increased to 60% owing to the lessening of mechanical losses.

Reduction of hydrocotarnine (5 *g.*) *to* (I) *by sodium, alcohol, and an inert solvent.*

Alcohol.	Solvent.	Sodium, g.	Yield, %.
Ethyl	Xylene	1·63	0
,,	,,	1·63	0
,,	Toluene	4·0	0
*iso*Amyl	Tetralin	4·0	12
,,	Xylene	4·0	32
,,	,,	2·0	mixture [1]
,,	,,	3·0	50
,,	Toluene	3·0	40 [2]
*iso*Propyl	Xylene	3·0	mixture [1]
,,	,,	3·8	45

[1] Mixture of hydrocotarnine and hydrohydrastinine; losses during fractional crystallisation of the hydrobromides prevent quantitative results being obtained.
[2] Two experiments.

The order of efficiency of the alcohols used (*iso*amyl > *iso*propyl ⩾ ethyl alcohol) is consistent with Birch's hypothesis (*J.*, 1945, 809), first applied to reductions by sodium in liquid ammonia and later extended to all reductions by sodium and an alcohol (Birch, *Nature*, 1946, **158**, 585). Decreasing the proton availability in the alcohol favours the reaction between the alcohol and the anion (*a*) relative to the proton and sodium reaction (*b*) :



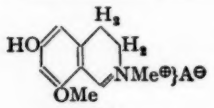
Birch (*Nature, loc. cit.*) considers that the liquid ammonia in reductions with sodium and liquid ammonia acts only as a solvent. In the present case the reaction takes a different course when carried out in this medium. Treatment of hydrocotarnine with sodium and liquid ammonia gives a practically quantitative yield of 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (III) by fission of the methylenedioxy-group. Under similar conditions hydrohydrastinine yields a mixture of 6- (V) and 7-hydroxy-2-methyl-1 : 2 : 3 : 4-tetrahydro-*iso*quinoline (VI).

In the presence of ammonium chloride, cotarnine hydrochloride is reduced by sodium and liquid ammonia to 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (III); if however, sodium hydroxide or ethoxide is previously added to the solution the cotarnine hydrochloride is reduced in the main to 1 : 6-dihydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro-*iso*quinoline characterised as the iodide, bromide, and picrate (VII) and also obtained from (III) and iodine in ethanol.

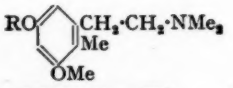
6 : 8-Dimethoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline was prepared from the tetrahydro-base (III) and diazomethane. One molecular proportion of methyl iodide and the base, with or without alkali, gave only 6-hydroxy-8-methoxy-2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolinium iodide. Prolonged methylation with excess of methyl iodide, potassium carbonate, and acetone gave 6 : 8-dimethoxy-1 : 2 : 3 : 4-tetrahydro-2 : 2-dimethyl*iso*quinolinium iodide.

Dr. A. J. Birch (private communication) reported that he had split benzyltrimethylammonium iodides to trimethylamine and toluene derivatives by means of sodium and liquid ammonia. During the present investigation this observation was extended to a number of 2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolinium iodides : 2-*o*-tolylethyldimethylamines were

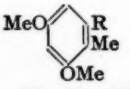
produced in the four examples studied. Thus the reduction follows the course of the catalytic reduction of these compounds (Emde and Kull, *Arch. Pharm.*, 1936, **274**, 173) instead of that of the Emde degradation with sodium amalgam (Emde, *Annalen*, 1912, **391**, 88) which leads to 2-vinylbenzyldimethylamines.



(VII.)



(VIII; R = H.)
(IX; R = Me.)



(X; R = Et.)
(XI; R = CH:CH$_2$.)

Hydrocotarnine methiodide or 6-hydroxy-8-methoxy-2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro-*iso*quinolinium iodide was reduced by sodium, alcohol, and liquid ammonia to dimethyl-2-(5′-hydroxy-3′-methoxy-2′-methylphenyl)ethylamine (VIII). In these cases the free phenolic group in the product protects the benzene ring from reduction by the sodium and alcohol (Birch, *J.*, 1944, 430). As the products from the fission of the 2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolinium iodide and 6 : 8-dimethoxy-2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydroisoquinolinium iodide, namely, dimethyl-2-*o*-tolylethylamine and dimethyl-2-(3′ : 5′-dimethoxy-2′-methylphenyl)ethylamine (IX), contain no protecting group it was necessary to omit the alcohol with a consequent diminution of the yield caused by the formation of high-boiling products. Trimethyl-2-(3′ : 5′-dimethoxy-2′-methylphenyl)ethylammonium iodide was split by sodium and liquid ammonia to 4 : 6-dimethoxy-2-ethyltoluene (X), but treatment with alkali gave 3 : 5-dimethoxy-2-methylstyrene (XI). According to Emde and Kull (*loc. cit.*) catalytic reduction is without effect on trimethylphenylethylammonium salts.

It is possible that the reductive splitting of these dimethyltetrahydro*iso*quinolinium salts may be of value in preparing definitely orientated *o*-ethyltoluene derivatives, etc.

Experimental.

Hydrocotarnine.—Cotarnine hydrochloride (30 g.) in water (40 c.c.) was reduced at room temperature/2 atmospheres by hydrogen and Adams's catalyst (50 mg.). The theoretical amount (3·1 l.) of hydrogen was taken up in 60—90 minutes. Hydrocotarnine hydrochloride was often precipitated towards the end of the reduction. Water (50 c.c.) was added, the solution filtered from the catalyst, and the base precipitated by aqueous ammonia. Two extractions with ether (70 c.c. each), and evaporation of the dried (Na_2SO_4) solution gave hydrocotarnine (95%), m. p. 55—56°, b. p. 182—183°/15 mm.

Hydrohydrastinine.—Hydrocotarnine (25 g.) and sodium (15 g.) in xylene (400 c.c.) in a three-necked flask fitted with stirrer, dropping funnel, and reflux condenser were heated on the sand-bath. The sodium in the boiling solution was finely dispersed by vigorous stirring and *iso*amyl alcohol (50 c.c.) run in. Stirring was continued for 20 minutes after the first vigorous reaction had abated, the solution was cooled, and the acid-soluble portion extracted with 10% hydrochloric acid (250 c.c.). The extract was basified and the non-phenolic bases extracted with ether (3 × 400 c.c.). The ether was evaporated off and the hydrohydrastinine separated from the hydrocotarnine by fractional crystallisation of the hydrobromides (Pyman and Remfry, *loc. cit.*). Hydrohydrastinine hydrobromide (m. p. 276—278°) was decomposed by aqueous potassium carbonate, the base extracted with ether and dried, and the solvent evaporated. Hydrohydrastinine (12·5 g., 60%), obtained as an oil, crystallised when kept; m. p. 61°.

6-*Hydroxy*-8-*methoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline.—(a) *From hydrocotarnine.* Hydrocotarnine (50 g.) was melted and dissolved in ether (50 c.c.). The solution was added to liquid ammonia (1·7 l.) containing ammonium chloride (30 g.) in a large Dewar flask. Sodium (20 g.) was added cautiously with mechanical stirring until a permanent blue colour was obtained. The ammonia was allowed to evaporate, water (400 c.c.) added, and the sodium salt of the phenolic base decomposed by a stream of carbon dioxide. After being set aside overnight, the crude 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (96%), m. p. 193—195°, was collected and recrystallised from ethyl acetate; m. p. 201—203°. The hydriodide had m. p. 223—224°.

(b) *From cotarnine hydrochloride.* Cotarnine hydrochloride (5 g.) and ammonium chloride (5 g.) in liquid ammonia (100 c.c.) were stirred by hand, and sodium (2·7 g.) was added in small pieces until a permanent blue colour was obtained. Evaporation of the ammonia, addition of water (40 c.c.), extraction of the non-phenolic products with ether, and saturation of the solution with ammonium acetate gave 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (50%), m. p. 180—185°. Recrystallisation from ethyl acetate gave a product having m. p. and mixed m. p. 202—203°.

6 : 8-*Dimethoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline.—6-Hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (2 g.) in absolute methanol (20 c.c.) was treated with diazomethane [from methylnitrosourea (10 g.) in ether (50 c.c.)] and set aside for 48 hours. The resulting solution was evaporated to dryness and partitioned between ether (40 c.c.) and 10% aqueous sodium hydroxide (20 c.c.). The ethereal extract was dried (Na_2SO_4); 6 : 8-*dimethoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline, purified by distillation, had b. p. 93°/0·1 mm. (Found: C, 69·1; H, 8·2. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·2%). The *picrate* forms rectangular orange prisms, m. p. 164°, from ethanol (Found: C, 49·5; H, 4·8. $C_{18}H_{20}O_9N_4$ requires C, 49·8; H, 4·6%).

6-Hydroxy-8-methoxy-2-methyl-3 : 4-dihydroisoquinolinium Iodide.—(*a*) Liquid ammonia (100 c.c.) was made " alkaline " by the addition of ethanol (8 c.c.), sodium (1 g.), and a few drops of water. When the sodium had reacted, cotarnine hydrochloride (10 g.) and then sodium (2·7 g.) were added slowly with hand-stirring. The ammonia was allowed to evaporate and the resultant solid dissolved in sodium hydroxide solution (60 c.c.). The sodium salt was decomposed by saturating the solution with ammonium acetate, and the product was extracted with ether (6 g., 79%). The viscous oil, left on the evaporation of the solvent, could not be induced to crystallise. The oil (3 g.) in 15% hydrochloric acid (10 c.c.) was mixed with sodium iodide (4 g.) in water (5 c.c.), giving *6-hydroxy-8-methoxy-2-methyl-3 : 4-dihydroisoquinolinium* iodide as colourless needles which lost water at 125° and, after two recrystallisations from water, had m. p. 206° (Found : C, 41·4; H, 4·4; N, 4·3. $C_{11}H_{14}O_3NI$ requires C, 41·4; H, 4·4; N, 4·4%). The *hydrobromide* recrystallises from ethanol in colourless needles as the hemihydrate, m. p. 222—224° (Found : C, 46·9; H, 5·0; N, 5·2. $C_{11}H_{14}O_3NBr,\frac{1}{2}H_2O$ requires C, 47·0; H, 5·3; N, 5·0%). The *picrate* was precipitated from hot ethanolic solutions and crystallised from glacial acetic acid as needles, m. p. 226—228° (Found : C, 49·1, 49·1; H, 4·0, 3·9. $C_{17}H_{14}O_9N_4$ requires C, 48·6; H, 3·8%).

(*b*) 6-Hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydroisoquinoline (1 g.) and potassium acetate (0·6 g.) in ethanol (10 c.c.) were boiled under reflux with iodine (1·4 g.) in ethanol (15 c.c.) until the iodine colour had largely disappeared. When the mixture was cooled in the ice-chest, 6-hydroxy-8-methoxy-2-methyl-3 : 4-dihydroisoquinolinium iodide (1·2 g.), m. p. 200—201°, was obtained; after one recrystallisation from water it had m. p. and mixed m. p. 202—204°.

6 : 8-Dimethoxy-2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydroisoquinolinium Iodide.—6-Hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydroisoquinoline (5 g.) in acetone (100 c.c.) was heated under reflux with methyl iodide (5 g.) and potassium carbonate (10 g.) for 12 hours. The solvent was removed, the residue was extracted twice with boiling ethanol (100, 20 c.c.), and the combined extracts were reduced to a quarter of their original volume. Cooling and adding ether precipitated the *dimethoxy-iodide* as an oil which solidified when kept. This was pure enough for the next reaction. Recrystallisation from glacial acetic acid gave white needles, m. p. 206—207° (Found : C, 44·4; H, 5·7; N, 3·5. $C_{13}H_{20}O_3NI$ requires C, 45·0; H, 5·7; N, 4·0%). The derived *picrate* crystallised from ethanol in yellow needles, m. p. 151° (Found : C, 50·9; H, 4·8; N, 12·1. $C_{19}H_{22}O_9N_4$ requires C, 50·7; H, 4·9; N, 12·4%).

Dimethyl-2-(3′ : 5′-dimethoxy-2′-methylphenyl)ethylamine.—To the preceding methiodide (6 g.) in liquid ammonia (80 c.c.) was added sodium (1 g.) in small pieces with stirring until a permanent blue colour was obtained. The ammonia was evaporated off and water added (30 c.c.) with gentle warming to remove the last traces of ammonia. The cooled solution was extracted twice with ether (25 c.c.), and the *product* (1·2 g.) purified twice by distillation; b. p. 104°/0·3 mm. (Found : C, 69·6; H, 9·4; N, 6·7. $C_{13}H_{21}O_2N$ requires C, 70·0; H, 9·4; N, 6·3%). The colourless liquid gave a *picrate* crystallising from glacial acetic acid in long yellow prisms, m. p. 177—179° (Found : C, 50·6; H, 5·2. $C_{19}H_{24}O_9N_4$ requires C, 50·4; H, 5·3%). To the base (1·2 g.) in ethanol (15 c.c.) was added methyl iodide (2 g.) and the whole boiled under reflux for 1 hour. The *methiodide* (1·8 g.) crystallised out when the mixture cooled, and, recrystallised from glacial acetic acid, had m. p. 242—243° (Found : C, 46·4; H, 6·7; N, 3·5. $C_{14}H_{24}O_2NI$ requires C, 46·0; H, 6·6; N, 3·8%).

3 : 5-Dimethoxy-2-methylstyrene.—The above methiodide (1 g.) was heated under reflux for 4 hours with 10% sodium hydroxide solution (20 c.c.). Trimethylamine was evolved. The cooled solution was extracted with ether. *3 : 5-Dimethoxy-2-methylstyrene*, purified by distillation, had b. p. 95°/0·7 mm. (Found : C, 73·8; H, 7·9. $C_{11}H_{14}O_2$ requires C, 74·2; H, 8·0%). A large amount of polymer was formed.

4 : 6-Dimethoxy-2-ethyltoluene.—The methiodide (1·8 g.) in liquid ammonia (100 c.c.) was treated with sodium until a permanent blue colour was obtained. The ammonia was evaporated and the residue partitioned between water (30 c.c.) and ether (20 c.c.). The oily *compound* left on evaporation of the ether was purified by distillation; it had b. p. 75°/0·4 mm. (Found : C, 73·0; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%).

Dimethyl-2-(5′-hydroxy-3′-methoxy-2′-methylphenyl)ethylamine.—Hydrocotarnine methiodide (or 6-hydroxy-8-methoxy-2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydroisoquinolinium methiodide) (8 g.) in liquid ammonia (100 c.c.) containing ethanol (5 c.c.) was treated with sodium until a permanent blue colour was obtained. The ammonia was evaporated and the residue taken up in water (30 c.c.). The sodium salt of the phenolic base was decomposed by carbon dioxide, and the product (3·5 g.) collected and dried. The *base*, which is soluble in ethanol and chloroform, was recrystallised from toluene; m. p. 168—169° (Found : C, 68·8; H, 9·2. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·1%). The *methiodide* crystallises from glacial acetic acid in glistening white plates, m. p. 197—198° (Found : C, 43·7; H, 6·5; N, 4·0. $C_{13}H_{22}O_2NI$ requires C, 44·4; H, 6·3; N, 4·0%). The *methopicrate* crystallises from ethanol or glacial acetic acid in orange needles, m. p. 215—216° (Found : C, 50·5; H, 5·2. $C_{19}H_{24}O_9N_4$ requires C, 50·5; H, 5·3%).

Dimethyl-2-o-tolylethylamine.—2 : 2-Dimethyltetrahydroisoquinolinium iodide (2·5 g.) was treated with sodium and liquid ammonia in the usual way. The *product* (1 g.) was extracted from the residue left by the evaporation of the ammonia with ether and was purified by distillation; b. p. 223—224°; it gave an aurichloride, m. p. 138°, methiodide, m. p. 250° and picrate, m. p. 136—137° (cf. Emde and Kull, *loc. cit.*, who cite base, b. p. 223—224°, aurichloride, m. p. 138°, methiodide, m. p. 250°, and picrate, m. p. 126—127°).

This work was carried out during the tenure of a maintenance allowance from the Department of Scientific and Industrial Research. The author thanks Professor Sir Robert Robinson, P.R.S., for help and encouragement, and Dr. A. J. Birch for his valuable advice on the theory and technique of reductions in liquid ammonia. The microanalyses were carried out by Drs. Weiler and Strauss, Oxford.

Dyson Perrins Laboratory, Oxford. [*Received, February 21st*, 1949.]

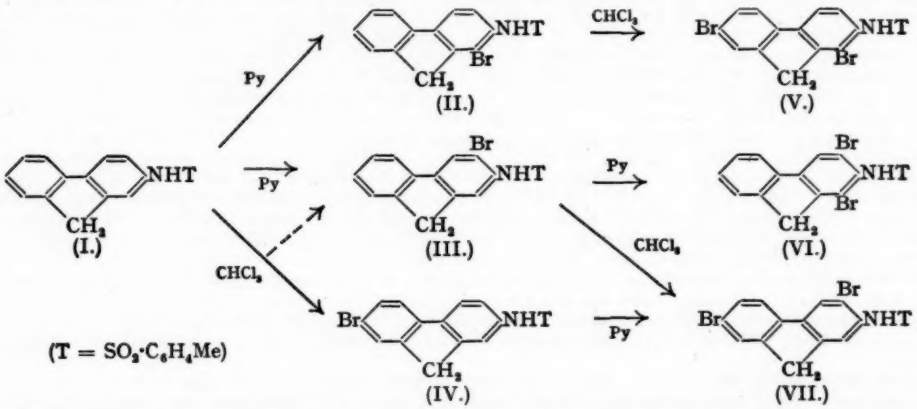
430. *Substitution Products of 2-Aminofluorene.*

By F. Bell and D. B. Mulholland.

The bromination and nitration of derivatives of 2-aminofluorene have been studied. The position entered is determined by both the entering group and the directing group (especially as modified by the nature of the solvent).

2-Aminofluorene is one of the most readily available derivatives of fluorene (*Org. Synth.*, Coll. Vol. II, 447), and several papers have already appeared on its substitution products. Eckert and Langecker (*J. pr. Chem.*, 1928, **118**, 263) by bromination of the base in acetic acid isolated a tribromo-derivative which could be oxidised to a tribromoaminofluorenone. It is, therefore, most probably 1 : 3 : 7-tribromo-2-aminofluorene. The nitration of 2-acetamidofluorene has been studied by Diels, Schill, and Tolson (*Ber.*, 1902, **35**, 3286), Eckert and Langecker (*loc. cit.*), and Koshits and Nikiforova (*J. Appl. Chem. U.S.S.R.*, 1940, **13**, 215). These authors agree that mononitration occurs at both positions 3 and 7 in the ratio of approximately 2·5 : 1. This result may be compared with the nitration of the closely related 4-acetamidodiphenyl entirely at position 3 (Fichter and Sulzberger, *Ber.*, 1904, **37**, 878).

Campbell, Anderson, and Gilmore (*J.*, 1940, 446), wishing to obtain fluorenes with a bromo-group in position 1, examined the bromination of both 2-toluene-*p*-sulphonamido- and 2-acetamido-fluorene. In each case only one product was isolated and this, by analogy with the nitro-derivative of 2-acetamidofluorene, was assumed to be the 3 : 7-dibromo-compound.*



In the present experiments we first re-examined the bromination of 2-aminofluorene in acetic acid solution and found that it was possible to isolate both a *monobromo-* and a *dibromo-*base, most probably the 3-bromo- and 1 : 3-dibromo-derivatives. Bromination of 2-acetamidofluorene gave a mixture of products from which it was possible to isolate 7-bromo- (70% yield) and 3 : 7-dibromo-2-acetamidofluorene. The position of entry of the bromine atom into 2-toluene-*p*-sulphonamidofluorene (I) is largely governed by the choice of chloroform or pyridine as a solvent. With one molecular proportion of bromine in chloroform there was produced a 60% yield of 7-bromo-2-toluene-*p*-sulphonamidofluorene (IV) (together with a small amount of 7-bromo-2-aminofluorene produced by hydrolysis) and impure *3-bromo-2-toluene*-p-*sulphonamidofluorene* (III). With 2 molecular proportions of bromine in chloroform there was obtained a 70% yield of the 3 : 7-dibromo-derivative (VII), identified by hydrolysis to the base and acetylation of this to 3 : 7-dibromo-2-acetamidofluorene. With 1 molecular proportion of bromine in pyridine there was obtained as the main product the 3-bromo-derivative and with 2 molecular proportions 1 : *3-dibromo-2-toluene*-p-*sulphonamidofluorene* (VI). A small amount of 1-bromo-2-toluene-*p*-sulphonamidofluorene (II) must be present in the crude 3-bromo-derivative, for on further bromination in chloroform it gave the 3 : 7-dibromo-derivative (main) together with 1 : *7-dibromo-2-toluene*-p-*sulphonamidofluorene* (V) (trace).

* The structure of derivatives of 2-aminofluorene has seldom been established with complete certainty. In particular, ring closures with 2-aminofluorenes which are usually assumed to occur at position 1 (see, *e.g.*, Diels and Staehlin, *Ber.*, 1902, **35**, 3275; Hughes, Lions, and Wright, *J. Proc. Roy. Soc. N.S. Wales*, 1938, **71**, 449; Neish, *Rec. Trav. chim.*, 1948, **67**, 349) might on general grounds be expected to occur at position 3.

Further bromination of (VII) gave 1 : 3 : 7-*tribromo*-2-*toluene*-p-*sulphonamidofluorene*, which was smoothly hydrolysed to the tribromo-base previously described by Eckert and Langecker.

Next, it was found that 2-*dimethylaminofluorene* behaved exactly as 4-dimethylaminodiphenyl (*J.*, 1926, 2709). With sodium nitrite in acetic acid it readily yielded the 3-*nitro*-derivative, which on further nitration gave a *dinitro*-2-*nitrosomethylaminofluorene*.

The nitration of 2-toluene-*p*-sulphonamidofluorene proceeded less smoothly than that of 4-toluene-*p*-sulphonamidodiphenyl (*J.*, 1926, 2708). Although the main product was the 3-*nitro*-derivative, it was accompanied by a small amount of a *trinitro*-derivative, which was alternatively prepared by the nitration of both 3- and 7-*nitro*-2-*toluene*-p-*sulphonamidofluorene*. It was not possible to prepare a dinitro-derivative and, further, since the nitro-toluene-*p*-sulphonamido-derivatives cannot be smoothly hydrolysed this gives a bad route to nitro-2-aminofluorenes.

Experimental.

(Analyses by Drs. Weiler and Strauss.)

2-Toluene-*p*-sulphonamidofluorene, prepared by interaction of 2-aminofluorene with toluene-*p*-sulphonyl chloride in pyridine, crystallised from acetic acid in needles, m. p. 161°. 7-*Nitro*-2-*toluene*-p-*sulphonamidofluorene*, from 7-nitro-2-aminofluorene (Diels, Schill, and Tolson, *loc. cit.*), crystallised from acetic acid in very pale yellow, glistening needles, m. p. 202° (Found: C, 62·9; H, 4·2. $C_{20}H_{16}O_4N_2S$ requires C, 63·2; H, 4·2%). 3-*Nitro*-2-*toluene*-p-*sulphonamidofluorene*, obtained in poor yield from 3-nitro-2-aminofluorene, formed a bright yellow crystalline powder, m. p. 198—201° (Found: N, 7·8. $C_{20}H_{16}O_4N_2S$ requires N, 7·4%).

Nitration of 2-*Toluene*-p-*sulphonamidofluorene*.—5 G. were dissolved in acetic acid (50 c.c.) by warming to 90° and the solution was rapidly cooled to 40°. Concentrated nitric acid (4 c.c.) in acetic acid (10 c.c.) was added to the resultant paste which rapidly dissolved to a clear solution that almost immediately began to fill with a bright yellow crystalline deposit of crude 3-nitro-2-toluene-*p*-sulphonamidofluorene (5 g.), m. p. 185—190°. This was filtered off and the mother-liquor poured into water. The resultant sticky mass was rubbed with acetic acid to dissolve away soluble impurities, and the residual solid recrystallised from bromobenzene. In this way 1 : 3 : 7-*trinitro*-2-*toluene*-p-*sulphonamidofluorene* was obtained as prisms, m. p. 233° with vigorous decomposition (Found: N, 12·1. $C_{20}H_{14}O_8N_4S$ requires N, 11·9%). It is almost insoluble in chloroform, toluene, or glycol, is sparingly soluble in acetone, dissolves in pyridine to yield a black solution, and recrystallises from acetic acid in needles containing solvent of crystallisation. It was alternatively prepared as follows.

(*a*) 3-Nitro-2-toluene-*p*-sulphonamidofluorene (1 g.), mixed with acetic acid (10 c.c.) and fuming nitric acid (2 c.c.), was heated on a steam-bath for 1 hour. The pasty mass was cooled and filtered, and the product (0·8 g.) purified by recrystallisation from bromobenzene.

(*b*) 7-Nitro-2-toluene-*p*-sulphonamidofluorene (1 g.) in hot acetic acid (15 c.c.) was treated with fuming nitric acid (1 c.c.) in acetic acid (2 c.c.). The liquid almost immediately became filled with a pale yellow precipitate (1 g.) of almost pure trinitro-derivative.

3-Nitro-2-toluene-*p*-sulphonamidofluorene was recovered unchanged after being boiled for 6 hours with an alcoholic solution of hydrogen chloride. It dissolved rapidly in cold concentrated sulphuric acid. The solution, on being poured into water and subsequently neutralised with aqueous ammonia furnished an orange-red product, separated by acetic acid into a sulphur-containing product (insoluble) and 3-nitro-2-aminofluorene, m. p. 202° (soluble in the hot acid but crystallising out on cooling). The base was readily acetylated by acetic anhydride containing a trace of sulphuric acid, to give 3-nitro-2-acetamidofluorene, glistening plates, m. p. 200°, in agreement with Hayashi and Nakayama (*J. Soc. Chem. Ind. Japan*, 1933, **36**, 127).

7-Nitro-2-aminofluorene is readily acetylated by acetic anhydride alone, yielding 7-nitro-2-acetamidofluorene, m. p. 250° [Aslak and Hamilton, *J. Amer. Chem. Soc.*, 1931, **53**, 746, give m. p. 250—253° (corr.)].

2-*Dimethylaminofluorene*.—This was expeditiously prepared in 50—60% yield by the methylation of 2-aminofluorene with dimethyl sulphate in the presence of sodium hydroxide. It crystallised from alcohol in lustrous plates, m. p. 179° (Found: C, 85·7; H, 7·2. $C_{15}H_{15}N$ requires C, 86·1; H, 7·2%), and dissolved readily in dilute hydrochloric acid. Interaction of this solution with sodium nitrite led to the precipitation of crude 3-nitro-2-dimethylaminofluorene, which was more conveniently prepared in the following way. Excess of sodium nitrite was added to a cooled solution of 2-dimethylaminofluorene (2 g.) in acetic acid (20 c.c.). The precipitated 3-*nitro*-2-*dimethylaminofluorene* (2·05 g.) recrystallised from alcohol in compact orange-red prisms, m. p. 100—103° (Found: C, 71·3; H, 5·7. $C_{15}H_{14}O_2N_2$ requires C, 70·9; H, 5·5%).

Dinitro-2-*nitrosomethylaminofluorene*.—Nitric acid (*d* 1·5; 1 c.c.) in acetic acid (2 c.c.) was added to a warm solution of 3-nitro-2-dimethylaminofluorene (1·5 g.) in acetic acid (10 c.c.). The liquid almost immediately began to deposit yellow needles (1·2 g.), m. p. 162° (decomp.). Recrystallisation from benzene gave *dinitro*-2-*nitrosomethylaminofluorene* as small, pale yellow needles, m. p. 165° (decomp.) (Found: C, 53·7; H, 3·3. $C_{14}H_9O_7N_5$ requires C, 53·5; H, 3·2%). This compound underwent partial decomposition on attempted recrystallisation from boiling acetic acid.

Bromination of 2-*Acetamidofluorene*.—Various solvents (acetic acid, chloroform, and carbon tetrachloride) and proportions of bromine (1—3 mols.) were tried, but in no case was it found possible to isolate a uniform product. The following is a typical experiment. Bromine (7 g., 2 mols.) was added to a warm solution of 2-acetamidofluorene (5 g.) in chloroform (60 c.c.). The liquid immediately became filled with a greenish-yellow precipitate which after 1 hour was filtered off (8·6 g.) and decomposed with aqueous ammonia. Repeated crystallisation from alcohol and then acetic acid gave a 70% yield of

7-bromo-2-acetamidofluorene, which formed needles, m. p. 228° alone or mixed with an authentic specimen prepared from 7-bromo-2-aminofluorene by acetylation (Found : C, 59·4; H, 4·0. Calc. for $C_{15}H_{12}ONBr$: C, 59·6; H, 4·0%). The chloroform mother-liquor, on evaporation, gave crude 3 : 7-dibromo-2-acetamidofluorene, which was obtained in snow-white glistening needles, m. p. 265° (decomp.), from bromobenzene (Found : C, 47·6; H, 2·9. Calc. for $C_{15}H_{11}ONBr_2$: C, 47·2; H, 2·9%). This compound was obtained in good yield by the further bromination of 3-bromo-2-acetamidofluorene in hot chloroform solution.

Bromination of 2-*Toluene*-p-*sulphonamidofluorene*.—(*a*) To 6·7 g. of this compound, dissolved in warm chloroform (50 c.c.), was added bromine (3·3 g., 1 mol.) in chloroform (3 c.c.), and the whole gently boiled until evolution of hydrogen bromide ceased. The hot solution was filtered from 7-bromo-2-aminofluorene hydrobromide (0·3 g.) and on cooling deposited needles (3·7 g.) of 7-bromo-2-toluene-*p*-sulphonamidofluorene, which formed feathery needles, m. p. 210°, from acetic acid (Found : Br, 19·6. Calc. for $C_{20}H_{16}O_2NBrS$: Br, 19·3%). This compound gave 7-bromo-2-aminofluorene, m. p. 144° (alone or mixed with an authentic sample), on dissolution in cold concentrated sulphuric acid. The chloroform mother-liquor from the bromination on evaporation furnished a brown plastic residue which on crystallisation from acetic acid furnished 3 g. of crude 3-bromo-2-toluene-*p*-sulphonamidofluorene (below).

(*b*) The experiment (*a*) was repeated with use of 2 mols. of bromine. After removal of a small amount of a hydrobromide, the crop, m. p. 195—201°, furnished 3 : 7-dibromo-2-toluene-*p*-sulphonamidofluorene in stellate clumps of fine needles, m. p. 203° (from acetic acid) (Found : Br, 31·9. Calc. for $C_{20}H_{15}O_2NBr_2S$: Br, 32·4%). Yield, 71%. This compound was alternatively prepared by the addition of bromine (1 mol.) to 7-bromo-2-toluene-*p*-sulphonamidofluorene dissolved in pyridine. Hydrolysis by dissolution in cold concentrated sulphuric acid gave 3 : 7-dibromo-2-aminofluorene, which crystallised from alcohol in needles, m. p. 148° (Campbell, Anderson, and Gilmore give 135°) (Found : C, 46·2; H, 3·0. Calc. for $C_{13}H_9NBr_2$: C, 46·0; H, 2·7%). Dissolution of this base in warm acetic anhydride gave 3 : 7-dibromo-2-acetamidofluorene (above).

(*c*) A solution of 3·35 g. of the sulphonamide in pyridine (*ca.* 15 c.c.) rapidly set to a semi-solid mass of the pyridine salt. To this was added, drop by drop, bromine (1 mol.) diluted with light petroleum (5 c.c.). The mixture was set aside for 3 hours and then decomposed with hydrochloric acid. The pasty product was filtered off and dissolved in hot ethanol. The pale yellow 3-*bromo*-2-*toluene*-p-*sulphonamidofluorene* (1·6 g.), m. p. 140—147°, after repeated crystallisation from benzene or acetic acid formed prisms, m. p. 155—156° (Found : Br, 19·6. $C_{20}H_{16}O_2NBrS$ requires Br, 19·3%). The alcoholic mother-liquor furnished only resinous material. This compound was readily brominated in chloroform to give 3 : 7-dibromo-2-toluene-*p*-sulphonamidofluorene in good yield.

(*d*) Experiment (*c*) was repeated with use of 2 mols. of bromine. The plastic product was freed from most of a non-crystallisable impurity (1·8 g.) by extraction with acetic acid. The residue, a brown powder, m. p. *ca.* 185° (2·8 g.), was fairly soluble in acetic acid and almost insoluble in ethanol, and was best crystallised from benzene. It then gave 1 : 3-*dibromo*-2-*toluene*-p-*sulphonamidofluorene* as prismatic needles, m. p. 214—215° (Found : Br, 31·8. $C_{20}H_{15}O_2NBr_2S$ requires Br, 32·4%). Dissolution in cold concentrated sulphuric acid gave 1 : 3-*dibromo*-2-*aminofluorene* in poor yield. The base crystallised from benzene in needles, m. p. 176—179° (Found : Br, 48·0. $C_{13}H_9NBr_2$ requires Br, 47·2%), and could be recovered unchanged from acetic anhydride or after treatment with toluene-*p*-sulphonyl chloride in pyridine.

Bromination of 2-*Aminofluorene*.—(*a*) The process of Eckert and Langecker (*loc. cit.*) gave tribromo-2-aminofluorene, which crystallised from xylene in colourless needles, m. p. 205°. This base did not react with toluene-*p*-sulphonyl chloride in pyridine, but with acetic anhydride gave 1 : 3 : 7-*tribromo*-2-*diacetamidofluorene*, which crystallised from acetic acid as a cotton-wool-like mass of needles, m. p. 241° (Found : C, 41·0; H, 2·6. $C_{15}H_{10}ONBr_3$ requires C, 40·6; H, 2·4%).

(*b*) Bromination in acetic acid with bromine (1 mol.) gave material from which it was impossible to isolate any pure individual.

(*c*) Bromine (6·4 g. ; 2 mols.) in acetic acid (8 c.c.) was added to a cooled solution of 2-aminofluorene (3·6 g.) in acetic acid (72 c.c.). After 1 hour the separated material was filtered off, triturated with ammonia solution, filtered, and dried. It was then extracted with hot alcohol (70 c.c.). The residue (3·9 g.) was slightly impure 1 : 3-dibromo-2-aminofluorene [(*d*) above]. From the alcoholic extract was obtained a small amount of 3-(or 1-)*bromo*-2-*aminofluorene* as lustrous plates, m. p. 143° (Found : Br, 29·9. $C_{13}H_{10}NBr$ requires Br, 30·8%), greatly depressed in m. p. on admixture with 7-bromo-2-aminofluorene. It readily gave 3-(or 1-)*bromo*-2-*acetamidofluorene*, needles, m. p. 206—207°, from acetic acid (Found : C, 59·3; H, 4·0. $C_{15}H_{12}ONBr$ requires C, 59·6; H, 4·0%).

1 : 3 : 7-*Tribromo*-2-*toluene*-p-*sulphonamidofluorene*.—This was readily prepared by the bromination of 3 : 7-dibromo-2-toluene-*p*-sulphonamidofluorene in cold pyridine, although this compound was unaffected by bromine in chloroform. It crystallised from acetic acid in compact needles, m. p. 215° (Found : C, 42·3; H, 2·6. $C_{20}H_{14}O_2NBr_3S$ requires C, 41·8; H, 2·4%), and was readily hydrolysed to the tribromo-base [(*a*) above] by dissolution in cold concentrated sulphuric acid.

Crude 3-bromo-2-toluene-*p*-sulphonamidofluorene (6 g.) in chloroform (30 c.c.) was treated with bromine (1 mol.) and heated until evolution of hydrogen bromide ceased. The solution was filtered from 1 : 3 : 7-tribromo-2-aminofluorene hydrobromide (0·5 g.) and evaporated to dryness. The residue on crystallisation from acetic acid furnished 3 : 7-dibromo-2-toluene-*p*-sulphonamidofluorene (3·7 g.) [(*b*) above]. The mother-liquor, on fractional crystallisation, gave stout needles of 1 : 7-*dibromo*-2-*toluene*-p-*sulphonamidofluorene*, m. p. 202—203° depressed by admixture with either the 1 : 3- or 3 : 7-isomeride (Found : Br, 32·8. $C_{20}H_{15}O_2NBr_2S$ requires Br, 32·4%).

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431. *Studies in the Polyene Series. Part XXXI. The Synthesis of C_{18} and C_{19} Acids related to Vitamin A.*

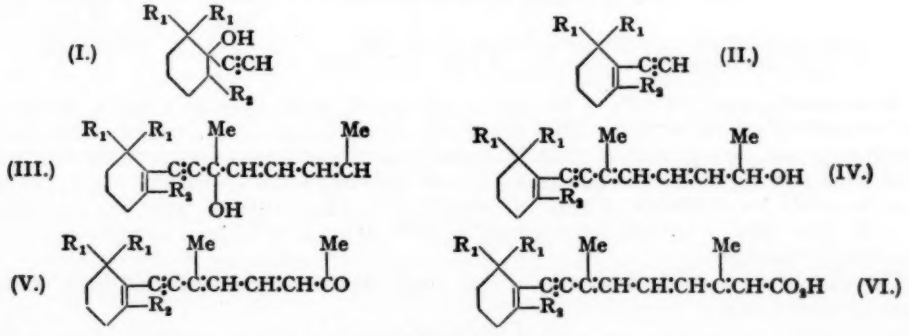
By Sir Ian Heilbron, E. R. H. Jones, D. G. Lewis, and B. C. L. Weedon.

The method previously developed for the preparation of the biologically active C_{17} acid (VI; $R_1 = R_2 = H$) has been applied to the synthesis of the C_{18} (VI; $R_1 = H$, $R_2 = Me$) and C_{19} (VI; $R_1 = Me$, $R_2 = H$) homologues.

Condensation of the ethynyl*cyclo*hexenes (II; $R_1 = H$, $R_2 = Me$) and (II; $R_1 = Me$, $R_2 = H$), obtained by dehydration of the corresponding ethynyl*cyclo*hexanols, with crotonylideneacetone gives the carbinols (III; $R_1 = H$, $R_2 = Me$) and (III; $R_1 = Me$, $R_2 = H$) which, on treatment with acids, undergo anionotropic rearrangement to the fully conjugated carbinols (IV; $R_1 = H$, $R_2 = Me$) and (IV; $R_1 = Me$, $R_2 = H$). The corresponding ketones, (V; $R_1 = H$, $R_2 = Me$) and (V; $R_1 = Me$, $R_2 = H$), prepared by Oppenauer oxidation of the carbinols, are condensed with methyl bromoacetate leading, after dehydration and hydrolysis, to the isolation of the crystalline acids (VI; $R_1 = H$, $R_2 = Me$) and (VI; $R_1 = Me$, $R_2 = H$). The latter acid, when administered orally as the sodium salt to young rats, shows small but definite growth-promoting properties.

A new synthetic approach to compounds related to vitamin A, and its application to the preparation of the biologically active C_{17} acid (VI; $R_1 = R_2 = H$), were described in Part XXV of this series (Heilbron, Jones, and Richardson, this vol., p. 287). As part of a comprehensive study of the relationship between molecular structure and growth-promoting activity of the vitamin-A type, the effect of introducing one and two methyl groups into the ring system, resulting in the formation of the C_{18} (VI; $R_1 = H$, $R_2 = Me$) and C_{19} (VI; $R_1 = Me$, $R_2 = H$) acids, has now been investigated.

Vapour-phase dehydration of both the solid and the liquid form of 2-methyl-1-ethynyl*cyclo*hexanol (I; $R_1 = H$, $R_2 = Me$) over a supported aluminium phosphate catalyst at 300—320° gave (*ca.* 40—55% yields) products consisting essentially of 2-methyl-1-ethynyl*cyclo*hex-1-ene (II; $R_1 = H$, $R_2 = Me$). The hydrocarbon obtained from the liquid carbinol was converted into 1-acetyl-2-methyl*cyclo*hexene (55% yield) by hydration, no other ketone being detected. On the other hand, hydration of the hydrocarbon from the solid carbinol, while giving 1-acetyl-2-methyl*cyclo*hexene as the major product (*ca.* 50%), yielded also an isomeric ketone (2 : 4-*dinitrophenylhydrazone*) (*ca.* 10%). Of the two dehydration products, both of which gave hexan-5-one-1-carboxylic acid (2 : 4-dinitrophenylhydrazone) on ozonolysis, that derived from the liquid carbinol appeared to be the more homogeneous and was therefore employed in the synthesis of the C_{18} acid (VI; $R_1 = H$, $R_2 = Me$) described below. Although the possibility that the starting material (II; $R_1 = H$, $R_2 = Me$) contained small amounts of other ethynyl*cyclo*hexenes cannot definitely be excluded, there can be no doubt as to the structure of the final C_{18} acid since the intermediate ketone (V; $R_1 = H$, $R_2 = Me$), which was purified by regeneration under mild conditions from a crystalline derivative, also gave hexan-5-one-1-carboxylic acid (2 : 4-dinitrophenylhydrazone) on ozonolysis.



While these investigations were in progress, Milas *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 1829) published an account of the dehydration of 2-methyl-1-ethynyl*cyclo*hexanol under conditions very similar to those described above. From the solid and the liquid form of the carbinol, products were obtained both of which gave hexan-5-one-1-carboxylic acid (unstated yields) on ozonolysis. On this evidence alone, these authors concluded that the ethynyl*cyclo*hexenes produced in the two cases had essentially the same composition.

6 : 6-*Dimethyl*-1-*ethynyl*cyclo*hex*-1-*ene* (II; R_1 = Me, R_2 = H) was readily obtained (65% yield) by vapour-phase dehydration of 2 : 2-dimethyl-1-ethynyl*cyclo*hexanol (I; R_1 = Me, R_2 = H) and was converted into 1-acetyl-6 : 6-dimethyl*cyclo*hexene on hydration.

Condensation of the Grignard reagents from the ethynyl*cyclo*hexenes (II; R_1 = H, R_2 = Me) and (II; R_1 = Me, R_2 = H) with crotonylideneacetone gave the *carbinols* (III; R_1 = H, R_2 = Me) and (III; R_1 = Me, R_2 = H), in 45 and 70% yields respectively, which when shaken with dilute sulphuric acid yielded the isomeric fully conjugated *carbinols* (IV; R_1 = H, R_2 = Me) and (IV; R_1 = Me, R_2 = H). The *ketones* (V; R_1 = H, R_2 = Me) and (V; R_1 = Me, R_2 = H) were prepared by oxidation of (IV) with aluminium *tert.*-butoxide and acetone and were purified by regeneration from the *semicarbazones* by the procedure of Heilbron, Jones, and O'Sullivan (*J.*, 1946, 866). Condensation of the ketones with methyl bromoacetate and zinc gave, after dehydration of the crude hydroxy-esters and hydrolysis, the crystalline *acids* (VI; R_1 = H, R_2 = Me), m. p. 167°, and (VI; R_1 = Me, R_2 = H), m. p. 171°, in 8 and 20% yield respectively.

		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Ethynyl*cyclo*hexene	(II; $R_1 = R_2 = H$)[1]	2230	12,500
		2280 *	9,500
	(II; R_1 = H, R_2 = Me)	2230	12,000
		2270	12,000
	(II; R_1 = Me, R_2 = H)	2230	9,000
		2280	9,000
Carbinol	(III; $R_1 = R_2 = H$)[1]	2270	39,000
		2370	30,000
	(III; R_1 = H, R_2 = Me)	2270	29,000
		2350 *	24,000
	(III; R_1 = Me, R_2 = H)	2230	23,000
		2310 *	9,500
Carbinol	(IV; $R_1 = R_2 = H$)[1]	2910	21,500
		3060	15,000
	(IV; R_1 = H, R_2 = Me)	2240	14,000
		2800	19,000
		2910	21,000
		3080	16,000
	(IV; R_1 = Me, R_2 = H)	2700	19,500
		2800	20,000
		2910	19,500
Ketone	(V; $R_1 = R_2 = H$)[1]	2450	18,000
		3350	23,000
	(V; R_1 = H, R_2 = Me)	2440	11,500
		3350	18,000
	(V; R_1 = Me, R_2 = H)	2420	12,500
		3360	20,500
Acid	(VI; $R_1 = R_2 = H$)[2]	2580	14,000
		3380	33,000
	(VI; R_1 = H, R_2 = Me)	3380	31,000
	(VI; R_1 = Me, R_2 = H)	2580	15,000
		3410	35,500

[1] Heilbron, Jones, and Richardson, this vol., p. 287.
[2] Heilbron, Jones, Julia, and Weedon, this vol., p. 1823.

* Inflexion.

When the C_{19} acid (VI; R_1 = Me, R_2 = H) was fed, as an aqueous solution of the sodium salt buffered at pH 10, in daily doses of 0·3 mg. to young rats on a vitamin-A-deficient diet, growth responses were produced which indicated that the acid possessed activity equivalent to about 5000 international units per gram, *i.e.*, of the same order as that of the C_{17} acid (VI; $R_1 = R_2$ = H) (*ca.* 1/1000th of that of vitamin A itself). Unexpectedly the C_{18} acid (VI; R_1 = H, R_2 = Me), when similarly tested in daily doses of 0·64 mg., exhibited no growth-promoting properties.

The various compounds described in this paper all showed the expected light absorption properties (see Table).

Experimental.

Light-absorption data were determined in ethanol except where stated otherwise. Data for most of the compounds described below are given in the Table. All the operations were carried out in an atmosphere of nitrogen.

2-*Methyl*-1-*ethynyl*cyclo*hexanol* (I; R_1 = H, R_2 = Me).—A solution of sodium acetylide in liquid ammonia (4 l.) was prepared from sodium (140 g.) and ferric nitrate (3 g.) by a method similar to that used by Heilbron, Jones, and Weedon (*J.*, 1945, 83). 2-Methyl*cyclo*hexanone (762 g.) in ether (500 c.c.) was added dropwise during 2 hours, and the mixture was stirred for a further 14 hours. The reaction

was terminated by the addition of ammonium chloride (400 g.), the ammonia was evaporated, and the crude product was isolated with ether in the usual way. Distillation gave 2-methyl-1-ethynyl*cyclo*hexanol (579 g.), b. p. 74—78°/14 mm., n_D^{20} 1·467—1·472. The carbinol was dissolved in pentane (600 c.c.), and the solution was set aside at −20° for 1 hour during which time a solid separated. Recrystallisation of the solid from pentane gave the solid isomer (128 g.) as needles, m. p. 58° [Milas *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1829, give m. p. 61—61·5° (corr.)]. The pentane solution, after removal of the solid, was evaporated and the residue distilled yielding the liquid isomer (431 g.), b. p. 74—77°/14 mm., n_D^{20} 1·4693 (Milas *et al.* give b. p. 84°/17 mm.).

2-*Methyl*-1-*ethynyl*cyclo*hex*-1-*ene* (II; R_1 = H, R_2 = Me).—The above carbinol (100 g.; liquid isomer) was distilled slowly (*ca.* 50 g./hr.) at 50 mm. through a hard-glass tube (60 × 2 cm.) containing a supported aluminium phosphate catalyst (for preparation see Heilbron, Jones, and Richardson, this vol., p. 287) maintained at 300—320°. The emergent gases were cooled and the liquid product was collected in a receiver cooled in ice–salt. After being shaken with a saturated solution of potassium chloride (100 c.c.) the organic layer was separated and dried ($CaCl_2$). Fractional distillation through a 40-cm. vacuum-jacketed Fenske column, at a reflux ratio of 20 : 1, gave 2-methyl-1-ethynyl*cyclo*hex-1-ene (47 g.), b. p. 67—69°/35 mm., n_D^{23} 1·4890 (Found: C, 89·6; H, 10·0. Calc. for C_9H_{12}: C, 90·0; H, 10·0%). Light absorption: Maximum, 2240 A.; $E^{1\%}_{1\,cm.}$, 520. A small portion (6 g.) of the hydrocarbon was added to an ammoniacal solution of silver nitrate (20 g.) in aqueous alcohol (95%; 400 c.c.), and the mixture was set aside at 20° for 30 minutes. The solid deposited was filtered, washed with water, alcohol, and ether, and dried under reduced pressure. The silver complex (4·7 g.) was added to a solution of potassium cyanide (20 g.) in water (30 c.c.), and the mixture was boiled under reflux until all the solid had disappeared (1 hour). After the mixture had cooled, the pure enyne (1·5 g.) was isolated by means of ether and distilled; b. p. 70°/35 mm., n_D^{15} 1·4937. Active hydrogen (Zerewitinoff): the hydrocarbon (75 mg.) evolved 15·5 c.c. of methane at 18°/769 mm., equivalent to 1·05 atom of active hydrogen per mole. Light absorption: Maxima, 2230 and 2270 A.; $E^{1\%}_{1\,cm.}$ 1000 and 1000; ε, 12,000. (Milas *et al.*, *loc. cit.*, give b. p. 63—65°/30 mm., n_D^{25} 1·4895; light absorption: Maximum, 2290 A.; ε, 10,000.)

Dehydration of 2-methyl-1-ethynyl*cyclo*hexanol (110 g.; solid isomer), in the manner described above, gave the hydrocarbon (45 g.), b. p. 85—88°/55 mm., n_D^{25} 1·4961. Light absorption: Maximum, 227 A.; $E^{1\%}_{1\,cm.}$, 625. A small portion (3 g.) of the product was converted into the silver complex (3·2 g.) and regenerated, in the manner described above, yielding the enyne (0·9 g.), b. p. 42—45°/9 mm., n_D^{17} 1·4945. Active hydrogen (Zerewitinoff): the hydrocarbon (78 mg.) evolved 13·8 c.c. of methane at 18°/770 mm., equivalent to 0·9 atom of active hydrogen per mole. Light absorption: Maximum, 2270 A.; $E^{1\%}_{1\,cm.}$, 100; ε, 12,000. (Milas *et al.*, *loc. cit.*, give b. p. 63·5—64°/30 mm., n_D^{25} 1·4883; light absorption: Maximum, 2290 A., ε, 11,500.)

Ozonolysis of 2-*Methyl*-1-*ethynyl*cyclo*hex*-1-*ene* (cf. Strain, *J. Biol. Chem.*, 1933, **102**, 137).—(*a*) A solution of the hydrocarbon (1·0 g.; from the liquid carbinol) in carbon tetrachloride (30 c.c.) was treated with ozonised oxygen for 5 hours. Glacial acetic acid (40 c.c.) was then added and the ozonolysis continued for a further 5 hours. Hydrogen peroxide (3 c.c. of 100-vol. solution) was added and the solution was kept for 14 hours. After removal of the acetic acid and carbon tetrachloride by steam-distillation, the residue was treated with a solution of 2 : 4-dinitrophenylhydrazine (1 g.) in sulphuric acid (10 c.c.; 30% w/v). The product was extracted with benzene, and the extract was washed with sulphuric acid (10% w/v) and water, dried, and evaporated, giving a red viscous liquid (0·89 g.). Trituration with methanol yielded a solid which crystallised from acetic acid–methanol in yellow plates (0·28 g.), m. p. 132° [Milas *et al.*, *loc. cit.*, give m. p. 132·6—133·1° (corr.) for the 2 : 4-dinitrophenylhydrazone of hexan-5-one-1-carboxylic acid] (Found: N, 17·45. Calc. for $C_{13}H_{16}O_6N_4$: N, 17·3%).

(*b*) Ozonolysis of the hydrocarbon (1·0 g.; from the solid carbinol), and treatment of the crude product with a solution of 2 : 4-dinitrophenylhydrazine in sulphuric acid in the manner described above, led to a red viscous oil (0·43 g.) which partly solidified. Recrystallisation of the solid from methanol gave the 2 : 4-dinitrophenylhydrazone (40 mg.), m. p. 131° undepressed on admixture with a specimen from (*a*).

1-*Acetyl*-2-*methyl*cyclo*hexene*.—(*a*) A mixture of 2-methyl-1-ethynyl*cyclo*hexene (2 g.; from the liquid carbinol), mercuric acetate (0·5 g.), glacial acetic acid (15 c.c.), ethanol (15 c.c.) and water (5 c.c.) was heated under reflux for 30 minutes. After cooling, the mixture was poured into water (100 c.c.), and the product was extracted with light petroleum (50 c.c.; b. p. 40—60°). The petroleum solution was washed with sodium hydrogen carbonate solution and water, dried, and evaporated. The residue (2 g.) was divided into 2 portions.

The first portion (0·5 g.) was treated with a solution of 2 : 4-dinitrophenylhydrazine (2 g.) and concentrated sulphuric acid (2 g.) in methanol (20 c.c.), the mixture was set aside for 2 hours at 20° and then poured into water (100 c.c.). The derivative was extracted with benzene and the extract was washed with dilute sulphuric acid (10% w/v) and water. After drying, the benzene solution was poured on a column of alumina, yielding one band. Elution of the latter with benzene, evaporation of the benzene solution, and crystallisation of the residue from ethyl acetate gave the 2 : 4-dinitrophenylhydrazone of 1-acetyl-2-methyl*cyclo*hexene (0·75 g.) as scarlet plates, m. p. 124°, undepressed on admixture with an authentic specimen (Braude, Jones, Sondheimer, and Toogood, this vol., p. 607, give m. p. 124—125°).

The second portion (1·5 g.) of the crude hydration product was treated with an excess of semicarbazide acetate in aqueous methanol (80%), the solution was warmed to 60° and set aside at 20° for 12 hours and at 0° for 16 hours. The solid deposited was recrystallised from methanol giving the semicarbazone of 1-acetyl-2-methyl*cyclo*hexene (1·4 g.) as plates, m. p. 215°, undepressed on admixture with an authentic specimen (Braude, Jones, Koch, Richardson, and Sondheimer, this vol., p. 1890, give m. p. 213°).

(*b*) The enyne (2 g.; prepared from the solid carbinol) was hydrated in the manner described above, and the product treated with an excess of semicarbazide acetate in aqueous methanol. The crude derivative (1·7 g.) on fractional crystallisation from methanol gave the semicarbazone of 1-acetyl-2-methyl*cyclo*hexene (1·2 g.), m. p. and mixed m. p. with an authentic specimen, 215°.

(*c*) The enyne (1 g.; prepared from the solid carbinol) was hydrated in the usual manner, and the product treated with methanolic 2 : 4-dinitrophenylhydrazine sulphate. The crude derivative (1·6 g.) was shown, by chromatographic separation on alumina, to contain *ca.* 80% of the 2 : 4-dinitrophenylhydrazone of 1-acetyl-2-methyl*cyclo*hexene and *ca.* 20% of an *isomer* which crystallised from methanol in orange plates, m. p. 113° (Found : N, 17·6. $C_{15}H_{18}O_4N_4$ requires N, 17·6%). Light absorption in chloroform (main band only) : Maximum, 3710 A.; ε, 23,500. Admixture of the two derivatives caused a marked depression of the m. p.

2 : 2-*Dimethyl*-1-*ethynyl*cyclo*hexanol* (I; R_1 = Me, R_2 = H).—2 : 2-Dimethyl*cyclo*hexanone (126 g.; regenerated from the semicarbazone, m. p. 200°) was condensed with sodium acetylide (from 25 g. of sodium) in liquid ammonia (1 l.) by the procedure described above. Distillation of the product gave the carbinol (128 g.), b. p. 86—89°/20 mm., n_D^{23} 1·4787 (Chanley, *J. Amer. Chem. Soc.*, 1948, **70**, 244, gives b. p. 113—113·5°/49 mm., n_D^{25} 1·4790) (Found : C, 79·0; H, 10·5. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%). The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 115° (Found : N, 8·4. $C_{17}H_{18}O_6N_2$ requires N, 8·1%).

6 : 6-*Dimethyl*-1-*ethynyl*cyclo*hex*-1-*ene* (II; R_1 = Me, R_2 = H).—The above carbinol (128 g.) was slowly distilled (*ca.* 40 g. per hour) at 60 mm. through a supported aluminium phosphate catalyst maintained at 300—320°. Isolation of the product in the usual way and distillation gave 6 : 6-*dimethyl*-1-*ethynyl*cyclo*hex*-1-*ene* (73 g.), b. p. 77—84°/35 mm., n_D^{20} 1·4792 (Found : C, 89·1; H, 10·85. $C_{10}H_{14}$ requires C, 89·5; H, 10·5%). Light adsorption : Maximum, 2240 A.; $E^{1\%}_{1\,cm.}$, 610. A small portion (4 g.) was converted into the silver complex (4·9 g.), and the enyne regenerated in the usual way giving an oil (1·3 g.), b. p. 86—88°/60 mm., n_D^{18} 1·4873. Active hydrogen (Zerewitinoff) : the enyne (72 mg.) evolved 13·4 c.c. of methane at 18°/769 mm., equivalent to 1·05 atoms of active hydrogen per mole. Light absorption : Maxima, 2230 and 2280 A.; $E^{1\%}_{1\,cm.}$, 680 and 680; ε, 9000.

1-*Acetyl*-6 : 6-*dimethyl*cyclo*hexene*.—A solution of the above hydrocarbon (0·6 g.) and mercuric acetate (0·25 g.) in a mixture of glacial acetic acid (7·5 c.c.), ethanol (7·5 c.c.), and water (2·5 c.c.) was heated under reflux for 30 minutes. After cooling, the mixture was poured into dilute sulphuric acid (10% w/v). The product was isolated in the usual manner with light petroleum (b. p. 40—60°) and converted into the semicarbazone which crystallised from methanol in plates (0·35 g.), m. p. 201°, undepressed on admixture with an authentic specimen of 1-acetyl-6 : 6-dimethyl*cyclo*hexene semicarbazone (Chanley, *loc. cit.*, gives m. p. 201—201·5°).

1-(2′-*Methyl*cyclo*hex*-1′-*enyl*)-3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (III; R_1 = H, R_2 = Me).—2-Methyl-1-ethynyl*cyclo*hex-1-ene (20 g.) in ether (20 c.c.) was added dropwise to a solution of ethylmagnesium bromide (prepared from 4 g. of magnesium) in ether (150 c.c.). After the addition was complete, the mixture was boiled under reflux for 1½ hours and then cooled and diluted with ether (600 c.c.). Crotonylideneacetone (18·2 g.) in ether (25 c.c.) was added dropwise to the stirred Grignard reagent at 0° during 1 hour, and the mixture was stirred for a further 45 minutes at 20°. The complex was decomposed by addition of ice and ammonium chloride (25 g.), and the product was isolated by means of ether in the usual way. Distillation from a short-path still gave 1-(2′-*methyl*cyclo*hex*-1′-*enyl*)-3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (17·6 g.) as a pale yellow viscous liquid, b. p. 80—90° (bath temp.)/10^{-5} mm., n_D^{18} 1·5400 (Found : C, 82·8; H, 9·85. $C_{14}H_{22}O$ requires C, 83·5; H, 9·6%). Light absorption : see Table.

8-(2′-*Methyl*cyclo*hex*-1′-*enyl*)-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (IV; R_1 = H, R_2 = Me).—A solution of the above carbinol (16 g.), and a trace of quinol, in ether (100 c.c.) was shaken for 16 hours with dilute sulphuric acid (500 c.c.; 1% w/v). Isolation of the product with ether in the usual way gave the crude carbinol (15·5 g.) as a viscous yellow oil. Distillation of a small portion yielded 8-(2′-*methyl*cyclo*hex*-1′-*enyl*)-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol*, b. p. 75—85° (bath temp.)/10^{-5} mm., n_D^{20} 1·5696 (Found : C, 83·2; H, 9·75. $C_{14}H_{22}O$ requires C, 83·5; H, 9·6%). Light absorption : see Table.

8-(2′-*Methyl*cyclo*hex*-1′-*enyl*)-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (V; R_1 = H, R_2 = Me).—A solution of the rearranged carbinol (12 g.; crude) and aluminium *tert.*-butoxide (30 g.) in dry acetone (500 c.c.) and dry benzene (750 c.c.) was boiled under reflux for 48 hours. After cooling, the mixture was poured into dilute sulphuric acid (4 l.; 2·5% w/v), and the organic layer separated. The aqueous solution was extracted with ether, and the combined ethereal extracts and benzene layer were washed with sodium hydrogen carbonate solution and water and dried. The solvents were evaporated, and the residue was dissolved in methanol and added to an excess of semicarbazide acetate in aqueous methanol (80%). The solution was warmed to 60° and then set aside for 24 hours at 20° and finally for 24 hours at 0°. The product which separated was recrystallised from methanol to give the *semicarbazone* (4·9 g.) as pale yellow plates, m. p. 186° (Found : N, 14·35. $C_{17}H_{23}ON_3$ requires N, 14·7%). Light absorption : Maximum, 3330 A.; ε, 40,000. Inflexion, 3480 A.; ε, 33,500.

The semicarbazone (4·4 g.; m. p. 186°) was suspended in light petroleum (200 c.c.; b. p. 80—100°) and dilute sulphuric acid (200 c.c.; 10% w/v), and the mixture was heated under reflux with vigorous stirring until all the solid had disappeared (3 hours). The product was isolated from the petroleum layer in the usual way and distilled, giving the *ketone* (2·9 g.) as a pale yellow oil, b. p. 80—90° (bath temp.)/10^{-5} mm., n_D^{18} 1·5945 (Found : C, 83·75; H, 9·3. $C_{14}H_{20}O$ requires C, 84·2; H, 8·8%). Light absorption : see Table.

The 2 : 4-*dinitrophenylhydrazone* was purified by adsorption on a column of alumina from benzene solution and crystallised from ethyl acetate–ethanol in purple needles, m. p. 175° (Found : N, 13·6. $C_{22}H_{24}O_4N_4$ requires N, 13·7%). Light absorption in chloroform (main band only) : Maximum 4110 A.; ε, 39,000.

Ozonolysis of the C_{14} *Ketone* (V; R_1 = H; R_2 = Me).—A solution of the regenerated ketone (237 mg.) in carbon tetrachloride (10 c.c.) was treated with ozonised oxygen for 2 hours; glacial acetic acid (10 c.c.) was added and the ozonolysis was continued for a further 2 hours. The crude product was converted into the 2 : 4-dinitrophenylhydrazone, which was isolated in the manner described above. Crystallisation from methanol gave the 2 : 4-dinitrophenylhydrazone of hexan-5-one-1-carboxylic acid as yellow plates (25 mg.), m. p. 131°, undepressed on admixture with the specimen described above.

8-(2′-*Methyl*cyclo*hexyl*)-6-*methyloctan*-2-*one*.—A solution of the above C_{14} ketone (265 mg.) in ethyl

acetate was shaken in hydrogen in the presence of platinic oxide (10 mg.) until absorption was complete (132 c.c. at 18°/773 mm., equivalent to 4·9 double bonds). After removal of the catalyst and solvent, distillation of the residue gave the saturated *ketone*, b. p. 110—115°/0·1 mm., n_D^{23} 1·4695 (Found : C, 80·65; H, 12·4. $C_{16}H_{30}O$ requires C, 80·7; H, 12·6%). The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in yellow plates, m. p. 39° (Found : N, 13·5. $C_{22}H_{34}O_4N_4$ requires N, 13·4%).

8-(2′-*Methyl*cyclo*hex*-1′-*enyl*)-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acid* (VI; R_1 = H, R_2 = Me).—A mixture of the regenerated ketone (V; R_1 = H, R_2 = Me) (2·9 g.), methyl bromoacetate (2·3 g.), activated zinc turnings (1 g.), mercuric chloride (0·1 g.), and dry benzene (15 c.c.) was heated under reflux for 1½ hours, during which time most of the zinc dissolved. The reaction mixture was then cooled, decanted from unchanged zinc, and shaken with dilute acetic acid (200 c.c.; 5% w/v). The benzene layer was separated, washed free from acid, dried, and evaporated. The residual orange-red oil (3·2 g.) was added to anhydrous oxalic acid (5 g.), and the mixture was heated at 95—100°/0·1 mm. for 2 hours. After the mixture had cooled, the crude unsaturated ester (1·7 g.) was isolated by extraction with light petroleum (b. p. 40—60°).

The ester was dissolved in methanolic potassium hydroxide (250 c.c.; 10% w/v) and kept for 48 hours at 20°. The solution was poured into water (2 l.), the non-saponifiable material was extracted with ether, and the aqueous layer was acidified with dilute phosphoric acid (150 c.c.; 50% w/v). The liberated acid was extracted with ether, and the ethereal solution was washed with water, dried, and evaporated. The residue, a viscous orange gum (0·9 g.), crystallised partly on trituration with methanol. Recrystallisation from the same solvent gave the *acid* (275 mg.) as pale yellow needles, m. p. 167° (Found : C, 80·25; H, 8·4. $C_{19}H_{22}O_2$ requires C, 80·0; H, 8·2%). Light absorption : see Table.

1-(6′ : 6′-*Dimethyl*cyclo*hex*-1′-*enyl*)-3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (III; R_1 = Me, R_2 = H).—A solution of crotonylideneacetone (41 g.) in ether (50 c.c.) was added slowly to 6 : 6-dimethyl-1-ethynyl-*cyclo*hexenylmagnesium bromide (prepared from 10 g. of magnesium and 50 g. of 6 : 6-dimethyl-1-ethynyl*cyclo*hex-1-ene) in ether (1,250 c.c.). The condensation and isolation of the product were effected by the procedure described above. The *carbinol* (63 g.) was obtained as a pale yellow oil, b. p. 80—90° (bath temp.)/10^{-5} mm., n_D^{21} 1·5232 (Found : C, 83·05; H, 10·2. $C_{17}H_{24}O$ requires C, 83·6; H, 9·8%). Light absorption : see Table.

8-(6′ : 6′-*Dimethyl*cyclo*hex*-1′-*enyl*)-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (IV; R_1 = Me, R_2 = H).—The above carbinol (60 g.), and a trace of quinol, in ether (200 c.c.) were shaken with dilute sulphuric acid (1·5 l.; 1% w/v) for 20 hours. Isolation of the product in the usual way gave the crude carbinol (58 g.) as a viscous oil. A small portion was distilled, yielding 8-(6′ : 6′-*dimethyl*cyclo*hex*-1′-*enyl*)-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol*, b. p. 85—95° (bath temp.)/10^{-5} mm., n_D^{21} 1·5432 (Found : C, 82·6; H, 10·1. $C_{17}H_{24}O$ requires C, 83·6; H, 9·8%). Light absorption : see Table.

8-(6′ : 6′-*Dimethyl*cyclo*hex*-1′-*enyl*)-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (V; R_1 = Me, R_2 = H).—A solution of the preceding rearranged carbinol (55 g.; crude) and aluminium *tert.*-butoxide (100 g.) in benzene (2·5 l.) and acetone (1·65 l.) was heated under reflux for 48 hours. The crude product was isolated and treated with an excess of semicarbazide acetate in aqueous methanol (80%) in the usual manner. The solid deposited was recrystallised from methanol giving the *semicarbazone* (23 g.) as pale yellow plates, m. p. 187° (Found : N, 14·0. $C_{18}H_{25}ON_3$ requires N, 14·05%). Light absorption : Maximum, 3360 A.; ε, 42,500. Inflexion, 3470 A.; ε, 36,000.

Regeneration from the semicarbazone (15 g.; m. p. 187°) by the procedure described above gave the *ketone* (9 g.) as a pale yellow oil, b. p. 80° (bath temp.)/10^{-5} mm., n_D^{20} 1·5937 (Found : C, 84·5; H, 9·45. $C_{17}H_{22}O$ requires C, 84·3; H, 9·1%). Light absorption : see Table. The 2 : 4-*dinitrophenylhydrazone* was purified by adsorption on alumina from benzene solution and crystallised from ethyl acetate in dark red leaflets, m. p. 187° (Found : N, 13·35. $C_{23}H_{26}O_4N_4$ requires N, 13·3%). Light absorption in chloroform (main band only) : Maximum, 4110 A.; ε, 42,000.

8-(2′ : 2′-*Dimethyl*cyclo*hexyl*)-6-*methyloctan*-2-*one*.—A solution of the above ketone (2·1 g.) in ethyl acetate (25 c.c.) was shaken in hydrogen in the presence of platinic oxide (0·1 g.) until absorption was complete (932 c.c. at 14°/765 mm.; equivalent to 4·8 double bonds). After removal of the catalyst and solvent, distillation of the residue gave the saturated *ketone* (1·9 g.), b. p. 106—108°/0·1 mm., n_D^{20} 1·4913 (Found : C, 80·9; H, 12·3. $C_{17}H_{32}O$ requires C, 81·0; H, 12·7%). The 2 : 4-*dinitrophenylsemicarbazone* crystallised from alcohol in yellow needles, m. p. 171° (Found : N, 14·65. $C_{24}H_{37}O_5N_5$ requires N, 14·75%).

8-(6′ : 6′-*Dimethyl*cyclo*hex*-1′-*enyl*)-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acid* (VI; R_1 = Me, R_2 = H).—The regenerated ketone (V; R_1 = Me, R_2 = H) (7·5 g.) was condensed with methyl bromoacetate (6 g.) and zinc (2·5 g.) in benzene (75 c.c.), and the resulting crude hydroxy-ester was dehydrated and hydrolysed in the usual manner, giving the crude acid (3·4 g.) as a viscous orange gum which partly solidified on trituration with light petroleum (b. p. 40—60°). Recrystallisation of the solid from methanol yielded the *acid* (1·72 g.) as pale yellow prisms, m. p. 171° (Found : C, 80·15; H, 8·4. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·4%). Light absorption : see Table.

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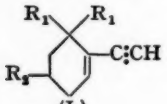
432. *Studies in the Polyene Series. Part XXXII. Further Syntheses of Analogues of β-Ionone.*

By Sir Ian Heilbron, E. R. H. Jones, J. B. Toogood, and B. C. L. Weedon.

In continuation of the schemes previously outlined for the preparation of compounds with modified β-ionone structures, 4-methyl-1-ethynyl*cyclo*hex-1-ene (I; $R_1 = H$, $R_2 = Me$) and 6 : 6-dimethyl-1-ethynyl*cyclo*hex-1-ene (I; $R_1 = Me$, $R_2 = H$) have been converted into the acetylenic ketones (II) which, on partial hydrogenation, yielded the diene ketones (III).

Developing the schemes previously described (Heilbron, Jones, Richardson, and Sondheimer, this vol., p. 737; Heilbron, Jones, Toogood, and Weedon, this vol., p. 1827) for the synthesis of analogues of β-ionone (IV), the diene ketones (III; $R_1 = H$, $R_2 = Me$) and (III; $R_1 = Me$, $R_2 = H$) have been prepared. As has already been reported (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, this vol., 1890), measurements of the light-absorption properties of these and related compounds have been of considerable value in revealing a plausible explanation for certain anomalies in the corresponding data for β-ionone.

Vapour-phase dehydration of 4-methyl-1-ethynyl*cyclo*hexanol over a supported aluminium phosphate catalyst at 300—310° (cf. Heilbron, Jones, and Richardson, this vol., p. 287) readily gave 4-*methyl*-1-*ethynyl*cyclo*hex*-1-*ene* (I; $R_1 = H$, $R_2 = Me$) in 75% yield. By condensation of the Grignard reagents derived from this hydrocarbon and from 6 : 6-dimethyl-1-ethynyl*cyclo*hex-1-ene (I; $R_1 = Me$, $R_2 = H$) (Heilbron, Jones, Lewis, and Weedon, preceding paper) with acetic anhydride at −60°, the acetylenic *ketones* (II; $R_1 = H$, $R_2 = Me$) and (II; $R_1 = Me$, $R_2 = H$) were obtained in 55 and 85% yield, respectively. Partial hydrogenation of the latter in the presence of a quinoline-poisoned palladium–charcoal catalyst gave the β-ionone analogues, 4-(4′-*methyl*cyclo*hex*-1′-*enyl*)*but*-3-*en*-2-*one* (III; $R_1 = H$, $R_2 = Me$) and 4-(6′ : 6′-*dimethyl*cyclo*hex*-1′-*enyl*)*but*-3-*en*-2-*one* (III; $R_1 = Me$, $R_2 = H$), which were isolated in 40 and 5% yield, respectively, after regeneration from the *semicarbazones*.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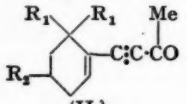
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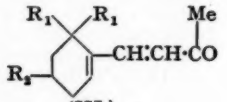
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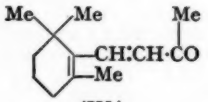

(IV.)

The light-absorption properties of the diene ketones (III; $R_1 = H$, $R_2 = Me$) and (III; $R_1 = Me$, $R_2 = H$) have been discussed previously (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *loc. cit.*), and the data for the acetylenic compounds described in this paper are very similar to those of the corresponding *cyclo*hexenyl analogues (see Table).

Experimental.

Light absorption measurements were determined in ethanol, except where stated otherwise, and the data are given in the Table. All the operations were performed in an atmosphere of nitrogen.

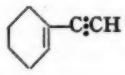
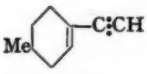
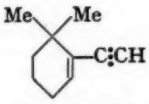
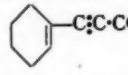
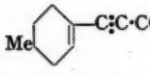
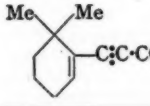
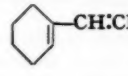
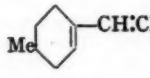
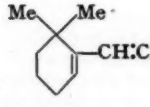
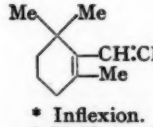
4-*Methyl*-1-*ethynyl*cyclo*hexanol*.—A solution of 4-methyl*cyclo*hexanone (156 g.) in ether (300 c.c.) was added dropwise during 2 hours to a solution of sodium acetylide [prepared from sodium (32 g.) by the procedure of Heilbron, Jones, and Weedon, *J.*, 1945, 83] in liquid ammonia (2 l.). After the mixture had been stirred for a further 5 hours, the reaction was terminated by the gradual addition of ammonium chloride (80 g.), and the ammonia evaporated. Isolation of the product in the usual way gave 4-methyl-1-ethynyl*cyclo*hexanol (118 g.), b. p. 100—103°/20 mm., m. p. 20° (Rupe and Kuenzy, *Helv. Chim. Acta*, 1931, **14**, 701, give b. p. 73—75°/10 mm., m. p. 20°).

4-*Methyl*-1-*ethynyl*cyclo*hex*-1-*ene* (I; $R_1 = H$, $R_2 = Me$).—The above carbinol (40 g.) was slowly distilled (*ca.* 40 g./hr.) at 110—120° (bath temp.)/18 mm. through a Pyrex tube (70 × 2 cm.) maintained at 300—310° and containing a supported aluminium phosphate catalyst (prepared according to Heilbron, Jones, and Richardson, *loc. cit.*). The emergent gases were condensed in air- and water-condensers, and the product was collected in a flask cooled in ice–salt. After the water produced had been separated, the crude product was distilled and the fraction boiling below 80°/50 mm. was dried ($CaCl_2$) and fractionated, to give 4-*methyl*-1-*ethynyl*cyclo*hex*-1-*ene* (22 g.) as a colourless mobile liquid, b. p. 71·5°/40 mm., n_D^{18} 1·4836 (Found : C, 89·5; H, 10·55. C_9H_{12} requires C, 89·9; H, 10·1%). By distillation of the high-boiling residue, 4-methyl-1-ethynyl*cyclo*hexanol (7 g.) was recovered.

The hydrocarbon (2·133 g.) in methyl acetate (15 c.c.) was shaken in hydrogen in the presence of platinic oxide catalyst until absorption ceased. Hydrogen absorbed was 1160 c.c. at 20°/770 mm., equivalent to 2·75 double bonds.

4-(4′-*Methyl*cyclo*hex*-1′-*enyl*)*but*-3-*yn*-2-*one* (II; $R_1 = H$, $R_2 = Me$).—A solution of 4-methyl-1-ethynyl*cyclo*hex-1-ene (30 g.) in dry ether (50 c.c.) was added dropwise to an ethereal solution of ethylmagnesium chloride (from 6·1 g. of magnesium), and the mixture heated under reflux for 2 hours. After cooling, the ethereal suspension of the Grignard reagent was slowly added with stirring to a solution

of acetic anhydride (26 g.) in ether (100 c.c.) at −60°. When addition was complete, the stirring was continued at −60° for an hour, and then the temperature of the mixture was allowed to rise to 20° during 2 hours. Ice was added, and the ethereal solution was separated, washed free from acid and dried.

			2 : 4-Dinitrophenylhydrazone. ‡		Semicarbazone.	
	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
 —C:CH [1]	2230 2280 *	12,500 9,500				
 —C:CH	2250	11,500				
 —C:CH [2]	2230 2280	9,000 9,000				
 —C:C·CO·Me [1]	2720 2220	11,000 6,000	3700	30,500	2820 2880 *	16,500 15,500
 —C:C·CO·Me	2710	11,000	3860 †	31,000	2820 2910 *	19,000 17,000
 —C:C·CO·Me	2710 2770 *	11,500 10,500	3790 †	27,500	2820 2910	16,000 15,000
 —CH:CH·CO·Me [3]	2810 2730 *	20,000 18,500	3950 †	32,000	2900 3000 *	35,000 32,000
 —CH:CH·CO·Me	2790 2730	23,000 23,000	3930 †	34,500	2910 3000 *	37,000 35,000
 —CH:CH·CO·Me	2810 2280 2910 *	13,000 4,000 12,500	3930 †	31,500	2910 2820	30,500 29,500
 —CH:CH·CO·Me [4]	2960 2230	10,700 6,500	3880 †	27,500	2820	22,300

* Inflexion. † In chloroform. ‡ Main band only.
[1] Heilbron, Jones, and Richardson, *loc. cit.* [2] Heilbron, Jones, Lewis, and Weedon, *loc. cit.*
[3] Heilbron, Jones, Richardson, and Sondheimer, *loc. cit.*
[4] Braude, Jones, Koch, Richardson, Sondheimer and Toogood, *loc. cit.*

Distillation gave recovered 4-methyl-1-ethynyl*cyclo*hex-1-ene (8·3 g.), b. p. 60—65°/20 mm., and 4-(4′-*methyl*cyclo*hex*-1′-*enyl*)*but*-3-*yn*-2-*one* (15·5 g.) as a mobile liquid having a pleasant odour, b. p. 59°/10^{-2} mm., n_D^{20} 1·5160 (Found: C, 81·65; H, 8·3. $C_{11}H_{14}O$ requires C, 81·45; H, 8·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in orange needles, m. p. 167° (Found: C, 59·6; H, 5·5. $C_{17}H_{18}O_4N_4$ requires C, 59·6; H, 5·3%). The *semicarbazone* crystallised from aqueous alcohol in clusters of fine needles, m. p. 155° (Found: C, 65·55; H, 7·9. $C_{12}H_{17}ON_3$ requires C, 65·7; H, 7·8%).

4-(4′-*Methyl*cyclo*hex*-1′-*enyl*)*but*-3-*en*-2-*one* (III; R_1 = H, R_2 = Me).—A solution of the above ketone (9·7 g.) in methyl acetate (35 c.c.) was shaken with hydrogen in the presence of a palladium–charcoal catalyst (1·0 g.; containing 0·5 g. of quinoline and 4% of Pd) (*cf.* Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 1947, **30**, 1911) until 1 molar proportion of hydrogen had been absorbed (1510 c.c. at 19°/753 mm.). After removal of the catalyst and solvent, fractionation gave a liquid (5·7 g.), b. p. 70—72°/10^{-2} mm., n_D^{22} 1·5300. Treatment with semicarbazide acetate (from semicarbazide hydrochloride, 6 g.) in methanol (30 c.c.) gave the *semicarbazone* (6·6 g.) which crystallised from alcohol in needles, m. p. 212° (Found: C, 65·3; H, 8·65. $C_{12}H_{19}ON_3$ requires C, 65·1; H, 8·65%).

The semicarbazone (6·03 g.) was heated under reflux for 5 hours with light petroleum (60 c.c.; b. p. 60—80°) and 2N-sulphuric acid (40 c.c.). Isolation of the product in the usual manner gave 4-(4′-

*methyl*cyclo*hex*-1′-*enyl*)*but*-3-*en*-2-*one* (3·78 g.) as a pleasant-smelling, very pale yellow liquid, b. p. 82°/5 × 10^{-2} mm., n_D^{24} 1·5330 (Found: C, 80·25; H, 9·95. $C_{11}H_{16}O$ requires C, 80·5; H, 9·8%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in dark red prisms, m. p. 205° (Found: C, 59·35, H, 5·55. $C_{17}H_{20}O_4N_4$ requires C, 59·25; H, 5·85%).

4-(4′-*Methyl*cyclo*hexyl*)*butan*-2-*one*.—A solution of the acetylenic ketone (II; R_1 = H, R_2 = Me) (4·55 g.) in methyl acetate (10 c.c.) was shaken with hydrogen in the presence of a platinic oxide catalyst until absorption ceased. Hydrogen absorbed at 16° and 755 mm. was 1800 c.c. equivalent to 2·7 double bonds. Removal of the catalyst and solvent, and distillation of the residue, gave 4-(4′-*methyl*cyclo*hexyl*)*butan*-2-*one* (3·80 g.) as a pleasant-smelling liquid, b. p. 56—58°/10^{-2} mm., n_D^{17} 1·4610 (Found: C, 78·4; H, 11·6. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous alcohol in yellow plates, m. p. 95° (Found: C, 58·25; H, 6·45. $C_{17}H_{24}O_4N_4$ requires C, 58·55; H, 6·95%). The *semicarbazone* crystallised from aqueous methanol in plates, m. p. 163° (Found: C, 63·85; H, 9·65. $C_{12}H_{23}ON_3$ requires C, 63·95; H, 10·2%).

4-(6′ : 6′-*Dimethyl*cyclo*hex*-1′-*enyl*)*but*-3-*yn*-2-*one* (II; R_1 = Me; R_2 = H).—A solution of 6 : 6-dimethyl-1-ethynyl*cyclo*hex-1-ene (30 g.) (Heilbron, Jones, Lewis, and Weedon, *loc. cit.*) in dry ether (150 c.c.) was added dropwise to an ethereal solution of ethylmagnesium chloride (from 5·45 g. of magnesium), and the mixture was heated under reflux for 3½ hours. After cooling, the ethereal suspension of the Grignard reagent was slowly added with stirring to a solution of acetic anhydride (46 g.) in ether (200 c.c.) at −60°. The temperature of the mixture was maintained at −60° for 1 hour and then allowed to rise to 10°. Ice was added, and the ethereal layer was separated, washed free of acid, and dried. Distillation gave (i) recovered 6 : 6-dimethyl-1-ethynyl*cyclo*hex-1-ene (13·7 g.), b. p. 60—62°/20 mm., and (ii) 4-(6′ : 6′-*dimethyl*cyclo*hex*-1′-*enyl*)*but*-3-*yn*-2-*one* (18·4 g.) as a pleasant-smelling liquid, b. p. 68°/0·05 mm., $n_D^{23\cdot5}$ 1·5110 (Found: C, 82·05; H, 9·35. $C_{12}H_{16}O$ requires C, 81·75; H, 9·15%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in orange needles, m. p. 148° (Found: C, 61·2; H, 5·6. $C_{18}H_{20}O_4N_4$ requires C, 60·8; H, 5·65%). The *semicarbazone* crystallised from aqueous methyl alcohol in needles, m. p. 115° (Found: C, 66·9; H, 8·1. $C_{13}H_{19}ON_3$ requires C, 66·9; H, 8·2%).

4-(6′ : 6′-*Dimethyl*cyclo*hex*-1′-*enyl*)*but*-3-*en*-2-*one* (III; R_1 = Me, R_2 = H).—A solution of the above ketone (10·3 g.) in methyl acetate (60 c.c.) was shaken with hydrogen in the presence of a palladium–charcoal catalyst (1·0 g.; containing 0·5 g. of quinoline and 4% of Pd) (*cf.* Isler *et al.*, *loc. cit.*) until 1 molar proportion of hydrogen had been absorbed (1435 c.c. at 20°/758 mm.). After removal of the catalyst and solvent, the product was distilled and collected in several fractions (b. p. 52—70°/10^{-2} mm.) of which only that with b. p. 65—70°/10^{-2} mm., n_D^{22} 1·5060 (1·7 g.), gave a solid derivative on treatment with semicarbazide acetate (from semicarbazide hydrochloride, 1·5 g.) in methanol (10 c.c.). Recrystallisation of the solid from alcohol gave the *semicarbazone* (0·9 g.) in plates, m. p. 191° (Found: C, 66·35; H, 9·05. $C_{13}H_{21}ON_3$ requires C, 66·3; H, 9·0%).

The semicarbazone (0·7 g.) was heated under reflux for 30 minutes with light petroleum (50 c.c.; b. p. 60—80°) and 2N-sulphuric acid (75 c.c.). Isolation of the product as usual gave 4-(6′ : 6′-*dimethyl*-cyclo*hex*-1′-*enyl*)*but*-3-*en*-2-*one* (0·5 g.) as a pleasant-smelling, very pale yellow liquid, b. p. 62°/10^{-2} mm., n_D^{19} 1·5178 (Found: C, 80·55; H, 10·35. $C_{13}H_{18}O$ requires C, 80·85; H, 10·2%). The product was collected in 5 fractions which differed but slightly in their light-absorption intensities. The 2 : 4-*dinitrophenylhydrazone* crystallised in dark red plates from acetic acid, m. p. 153° (Found: C, 60·3; H, 6·15. $C_{19}H_{22}O_4N_4$ requires C, 60·45; H, 6·1%).

4-(2′ : 2′-*Dimethyl*cyclo*hexyl*)*butan*-2-*one*.—A solution of the acetylenic ketone (II; R_1 = Me, R_2 = H) (1·42 g.) in methyl alcohol (10 c.c.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (0·2 g.; 10% of Pd) until absorption ceased. Hydrogen absorbed at 20° and 770 mm. was 570 c.c., equivalent to 2·95 double bonds. Removal of the catalyst and solvent, and distillation of the residue, gave 4-(2′ : 2′-*dimethyl*cyclo*hexyl*)*butan*-2-*one* (1·2 g.), as a pleasant-smelling liquid, b. p. 60·5°/10^{-2} mm., n_D^{21} 1·4648 (Found: C, 78·9; H, 12·25. $C_{13}H_{24}O$ requires C, 79·05; H, 12·15%). The *semicarbazone* crystallised from methyl alcohol in needles, m. p. 186° (Found: C, 65·15; H, 10·05. $C_{13}H_{25}ON_3$ requires C, 65·2; H, 10·5%).

The authors thank the Rockefeller Foundation for a grant. One of them (J. B. T.) is indebted to the Department of Scientific and Industrial Research for a Maintenance Grant and to the Directors of Glaxo Laboratories Ltd. for financial assistance. Light-absorption data were determined by Dr. E. A. Braude.

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433. *Studies in the Polyene Series. Part XXXIII. The Preparation of 6-Methylocta-3 : 5 : 7-trien-2-one, a Key Intermediate for the Synthesis of Vitamin A and its Analogues.*

By G. W. H. Cheeseman, Sir Ian Heilbron, E. R. H. Jones, F. Sondheimer, and B. C. L. Weedon.

In the development of new approaches for the synthesis of vitamin A and its analogues, the key intermediate 6-methylocta-3 : 5 : 7-trien-2-one (II) has been prepared from readily available starting materials.

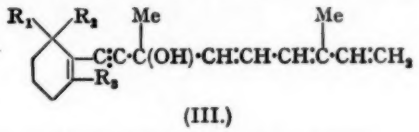
Condensation of crotonylideneacetone with acetylene gives the carbinol (VII) which, by partial hydrogenation and treatment of the resulting vinylcarbinol (VIII) with dilute acids, is isomerised to the triene carbinol (IX), Oppenauer oxidation of which yields the required ketone (II).

The diene carbinol (XIV) is obtained either by partial hydrogenation of (XII) and treatment of the divinyl carbinol (XIII) so formed with dilute acids, or alternatively by partial reduction of (XV). Oxidation of (XIV) with acetone and aluminium *tert.*-butoxide gives the ketone (II) directly.

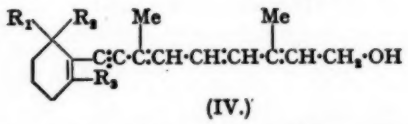
Schemes for the synthesis of vitamin A and its analogues, which involve the condensation of ethynyl*cyclo*hexenes with unsaturated aldehydes and ketones and the anionotropic rearrangement of the resulting carbinols to the fully conjugated isomers, were outlined in Part XXV of this series (Heilbron, Jones, and Richardson, this vol., p. 287; cf. Heilbron, *J.*, 1948, 386). Subsequent papers (Heilbron, Jones, Weedon, *et al.*, this vol., pp. 742, 2023) have described progress made along these lines. In view of the general nature of the rearrangement (cf. Jones, *Ann. Reports*, 1944, **41**, 148), it was to be expected that primary alcohols of the type (IV; R_1, R_2,

(I.)

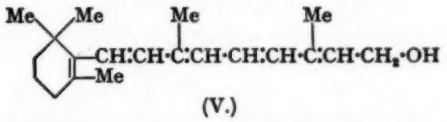
(II.)



(III.)



(IV.)



(V.)

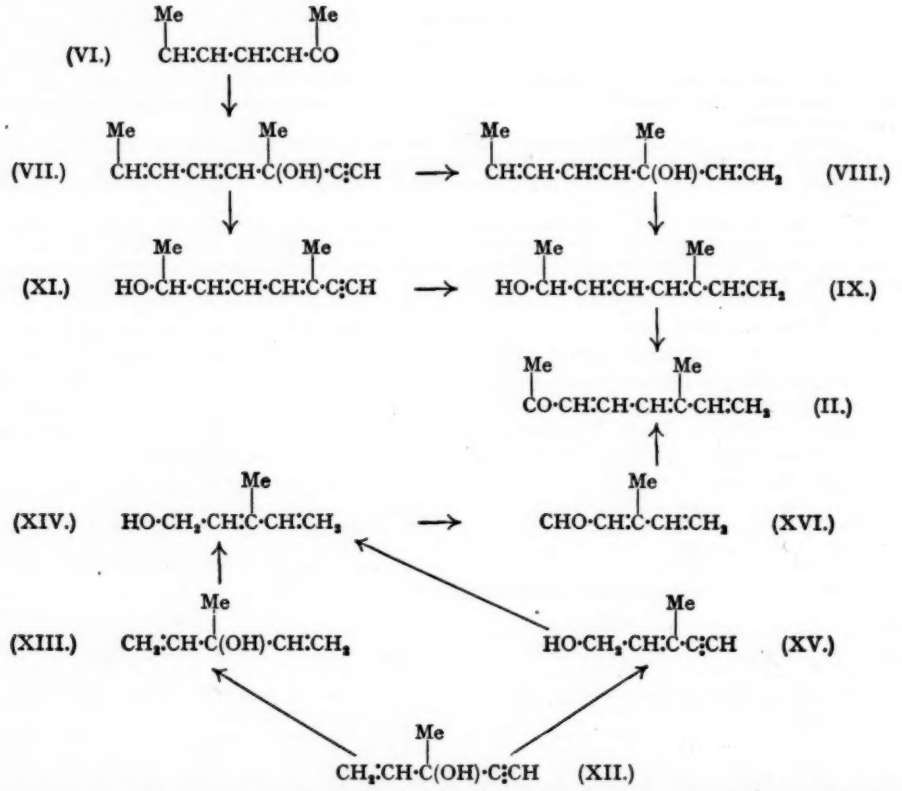
and R_3 = H or Me) could readily be prepared by condensation of the ethynyl*cyclo*hexenes (I; R_1, R_2, and R_3 = H or Me) with the hitherto unknown triene ketone (II) and rearrangement of the resulting tertiary carbinols (III; R_1, R_2, and R_3 = H or Me). It will be noted that these primary alcohols (IV) bear a close structural relation to vitamin A (V). The successful development of this synthetic scheme to give (IV; $R_1 = R_2 = R_3$ = H) is reported in the following publication in this series. This paper records the synthesis of the key intermediate (II) from the readily available materials, crotonylideneacetone (VI) and methyl vinyl ketone.

The ethynylcarbinol (VII), possessing the complete C_9 skeleton of (II), was readily obtained by treatment of crotonylideneacetone (VI) with 2 moles of lithium acetylide in liquid ammonia. The crude product was shown, by light-absorption measurements, to contain *ca.* 20% of unchanged ketone; after removal of the latter by conversion into the semicarbazone, 3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (VII), m. p. 19°, was obtained in an overall yield of 50%. With the exception of β-ionone (cf. Oroshnik, U.S.P. 2,425,201), this is believed to be the only case so far reported in which a conjugated diene ketone has been successfully converted into the corresponding ethynylcarbinol. When a large excess (4 mols.) of sodium acetylide (cf. Cymerman, Heilbron, and Jones, *J.*, 1945, 90) was used instead of lithium acetylide, extensive polymerisation occurred and the crude carbinol (VII) was isolated in only 25% yield.

Hydrogenation of (VII) proceeded smoothly in the presence of a palladium–calcium carbonate catalyst and, by interrupting the reaction after 1 mole of hydrogen had been absorbed, the *vinylcarbinol* (VIII) was obtained in 95% yield (cf. Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, 84; Cymerman, Heilbron, and Jones, *loc. cit.*). This carbinol exhibited light-absorption properties typical of a diene chromophore and very similar to those of (VII), indicating that reduction of the latter had occurred exclusively at the acetylenic linkage (see Table).

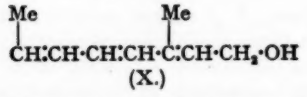
When shaken with 0·05% sulphuric acid, the vinylcarbinol (VIII) was isomerised to the fully conjugated isomer, 6-*methylocta*-3 : 5 : 7-*trien*-2-*ol* (IX) (cf. *idem*, *loc. cit.*), the structure

of which was established by complete hydrogenation and oxidation of the resulting saturated carbinol to the known 6-methyloctan-2-one (Heilbron, Jones, and Julia, this vol., p. 1430); no carboxylic acid was detected, as would have been the case had the rearrangement of (VIII) given any of the primary carbinol (X).

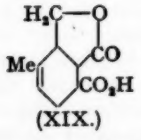


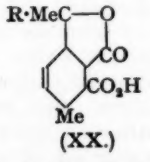
Oxidation of (IX) with acetone and aluminium *tert.*-butoxide or phenoxide yielded (65—80%) the required ketone, *6-methylocta-3 : 5 : 7-trien-2-one* (II) (*2 : 4-dinitrophenylhydrazone*; *semicarbazone*), with light-absorption properties similar to those of octatrienal. This ketone gave 6-methyloctan-2-one on hydrogenation.

The ethynylcarbinol (VII) underwent the expected anionotropic rearrangement when shaken with 1% sulphuric acid (cf. Heilbron, Jones, *et al.*, *J.*, 1943—1946) giving (90%) *6-methylocta-3 : 5-dien-7-yn-2-ol* (XI) from which the triene ketone (II), isolated as its 2 : 4-dinitrophenylhydrazone, was obtained by partial hydrogenation and oxidation of the resulting crude carbinol (IX). The structure of (XI) was confirmed by hydrogenation, followed by oxidation of the saturated product to 6-methyloctan-2-one.



(X.)


(XIX.)


(XX.)

The ketone (II) has also been synthesised from the acetylenic carbinol (XII), derived from methyl vinyl ketone (Cymerman, Heilbron, and Jones, *loc. cit.*), by the following routes. Partial hydrogenation of (XII) in the presence of a palladium–calcium carbonate catalyst yielded (60%) *3-methylpenta-1 : 4-dien-3-ol* (XIII), which when shaken with 1% sulphuric acid was converted into the conjugated *isomer* (XIV) in 25% yield. (XIV) was also obtained in 60% yield by partial hydrogenation of 3-methylpent-2-en-4-yn-1-ol (XV) (*idem*, *loc. cit.*). On oxidation of the diene carbinol (XIV) with acetone and aluminium *tert.*-butoxide, the initially

formed aldehyde (XVI) condensed with excess of acetone, giving the ketone (II) directly in an overall yield of 30% (cf. Heilbron *et al.*, *J.*, 1938, 175). The postulated intermediate (XVI) in this reaction was also prepared by the method of Heilbron, Jones, Julia, and Weedon (*loc. cit.*) and shown to give the ketone (II) on condensation with acetone.

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
CHMe:CH·CH:CH·CMe(OH)·C:CH (VII)	2270	26,500
CHMe:CH·CH:CH·CMe(OH)·CH:CH_2 (VIII)	2290	27,500
CH_2(OH)·CH:CMe·CH:CH_2 (XIV)	2280	24,500
CHMe(OH)·CH:CH·CH:CH_2 [1]	2230	28,000
CHMe(OH)·CH:CH·CH:CMe·C:CH (XI)	2600	35,500
	2640 *	32,000
	2690 *	27,500
CHMe(OH)·CH:CH·CH:CMe·CH:CH_2 (IX)	2590	32,500
	2670	40,500
	2770	32,500
CHMe(OH)·CH:CH·CH:CH·C:CH [2]	2600	34,000
	2470 *	24,500
	2730 *	24,500
Me·CO·CH:CH·CH:CMe·CH:CH_2 (II)	3080	31,500
CHO·CH:CH·CH:CH·CH:CHMe [3]	3060 †	41,000

* Inflexion. † In hexane.

[1] Heilbron, Jones, McCombie, and Weedon, *loc. cit.*

[2] Heilbron, Jones, and McCombie, *J.*, 1944, 134.

[3] Hausser, Smakula, Kuhn, and Hoffer, *Z. physikal. Chem.*, 1935, *B*, **29**, 371.

When treated with maleic anhydride, (XIV) behaved in the manner characteristic of conjugated dienols (Heilbron, Jones, McCombie, and Weedon, *loc. cit.*) and yielded the latonic *acid* (XIX). Similarly the *acids* (XX; R = C:CH) and (XX; R = CH:CH_2) were obtained from the carbinols (VII) and (VIII), respectively.

The various compounds described in this paper all exhibited the expected light-absorption properties (see Table).

Experimental.

All the operations were performed in an atmosphere of nitrogen. Light-absorption data were determined in ethanol except where stated otherwise. Data for most of the compounds described below are given in the Table.

3-Methylocta-4 : 6-dien-1-yn-3-ol (VII).—Liquid ammonia (4 l.) was poured into a 10-l. flask, provided with a gas-inlet tube and a mechanical stirrer and cooled in a carbon dioxide–alcohol bath. A vigorous stream of acetylene (*ca.* 3 l./min.) was bubbled into the stirred liquid, and lithium (30 g.), cut into small pieces, was added during 15 minutes. A vigorous evolution of hydrogen was observed, which soon stopped, indicating complete conversion of the lithium into the acetylide which was obtained as a milky suspension. The acetylene flow was reduced (to *ca.* 200 c.c./min.) and crotonylideneacetone (200 g.; b. p. 86°/24 mm., n_D^{21} 1·5210) in dry ether (800 c.c.) was added during 4 hours. The cooled mixture was stirred for a further 14 hours, and ammonium chloride (300 g.) was then gradually added. The ammonia was evaporated on the steam-bath, water and ether were added to the residue, and the ethereal layer was separated, washed with water, and dried ($MgSO_4$). The ethereal extract was evaporated, and the residue distilled giving a colourless liquid (203 g.), b. p. 72—78°/1 mm., n_D^{22} 1·5077. Light absorption: Maxima, 2280, 2700 A.; $E_{1\,cm.}^{1\%}$, 1900 and 400 respectively.

Semicarbazide hydrochloride (60 g.), dissolved in hot water (60 c.c.), was added to a solution of potassium acetate (70 g.) in methanol (300 c.c.). After the mixture had been cooled, the potassium chloride deposited was filtered off and the filtrate was added to the crude carbinol, described above, dissolved in methanol (500 c.c.). The solution was heated at 60° for a few minutes and set aside at room temperature overnight. The solution was then poured into water (2·5 l.) and light petroleum (800 c.c.; b. p. 40—60°), and the mixture shaken. This caused the precipitation of crotonylideneacetone semicarbazone which was filtered off. The aqueous layer was shaken with more light petroleum, and the combined petroleum extracts were dried ($MgSO_4$) and cooled to 0°, whereupon further crotonylideneacetone semicarbazone separated. The mixture of magnesium sulphate and semicarbazone was filtered off and washed with cooled light petroleum (b. p. 40—60°), and the filtrate evaporated. The residue was distilled giving *3-methylocta-4 : 6-dien-1-yn-3-ol* (126 g.), b. p. 68°/0·5 mm., m. p. 19°, n_D^{23} 1·5021, which contained no trace of ketonic material (Found: C, 79·7; H, 9·05. $C_9H_{12}O$ requires C, 79·35; H, 8·9%). Light absorption: see Table.

The carbinol (0·4 g.) and maleic anhydride (0·4 g.) were heated in benzene (5 c.c.) and then kept at room temperature overnight. The precipitated solid was recrystallised from water giving *6-methyl-3-(1′-hydroxy-1′-methylprop-2′-ynyl)cyclohex-4-ene-1 : 2-dicarboxylic acid 2→1′-lactone* (XX; R = CH:C) (0·5 g.) as plates, m. p. 213—215° (Found: C, 66·85; H, 5·8. $C_{13}H_{14}O_4$ requires C, 66·65; H, 6·0%).

3-Methylocta-1 : 4 : 6-trien-3-ol (VIII).—The acetylenic carbinol (VII) (112 g.) in methyl acetate (400 c.c.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (5 g.; 6% of Pd), with periodic cooling, until 20·2 l. of hydrogen had been absorbed at 22°/767 mm., equivalent to 1 molar proportion. Removal of the catalyst and solvent, followed by fractionation of the residue,

gave 3-*methylocta*-1 : 4 : 6-*trien*-3-*ol* (106·5 g.), b. p. 65—67°/0·8 mm., n_D^{20} 1·4975 (Found : C, 78·1; H, 10·15. $C_9H_{14}O$ requires C, 78·2; H, 10·2%). Light absorption : see Table.

The carbinol (0·3 g.) and maleic anhydride (0·3 g.) were heated in benzene (3 c.c.) and then kept at room temperature overnight. The precipitated solid was crystallised from water giving 6-*methyl*-3-(1′-*hydroxy*-1′-*methylprop*-2′-*enyl*)-cyclo*hex*-4-*ene*-1 : 2-*dicarboxylic acid* 2→1′-*lactone* (XX; R = CH_2:CH) (0·3 g.) as plates, m. p. 192—193° (Found : C, 66·15; H, 6·85. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·85%).

6-*Methylocta*-3 : 5 : 7-*trien*-2-*ol* (IX).—The above carbinol (VIII) (105 g.) was shaken with dilute sulphuric acid (1·5 l.; 0·05% w/v) in the presence of a trace of quinol for 90 minutes. The product was extracted with ether, washed with sodium hydrogen carbonate solution and water, and the dried ($MgSO_4$) extract evaporated. Distillation of the residue gave 6-*methylocta*-3 : 5 - 7-*trien*-2-*ol* (63 g.; 60%), b. p. 86—88°/0·7 mm., n_D^{22} 1·5501—1·5562 (the product was collected in several fractions which showed only slight differences in light-absorption intensity). Light absorption : see Table. A large amount of a transparent polymer was also obtained. When stronger acid was employed, this polymer was the main product. In smaller-scale experiments in which a solution of the carbinol (VIII) (*ca.* 50 g.) in ether (*ca.* 100 c.c.) was shaken with dilute sulphuric acid (0·05% w/v) for 3 hours, the yield of the rearranged carbinol was increased to 75%.

6-*Methyloctan*-2-*one*.—The above rearranged carbinol (1·56 g.) in acetone (10 c.c.) was shaken in hydrogen in the presence of platinic oxide until absorption was complete (820 c.c. of hydrogen absorbed at 20°/761 mm., equivalent to 2·95 double bonds). The catalyst was filtered off, and a large excess of chromic acid in dilute sulphuric acid was added to the filtrate. The mixture was heated on the steam-bath for 15 minutes, and the product was isolated by means of ether in the usual manner. The neutral fraction yielded 6-methyloctan-2-one (1·2 g.), b. p. 87°/24 mm., n_D^{21} 1·4225 (Heilbron, Jones, and Julia, this vol., p. 1430, give b. p. 70°/10 mm., n_D^{18} 1·4250). The semicarbazone crystallised from aqueous methanol in plates, m. p. 128°, undepressed on admixture with an authentic specimen (*idem*, *loc. cit.*, give m. p. 131°). The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous methanol in orange plates, m. p. 61—62° (Found : N, 17·45. $C_{15}H_{22}O_4N_4$ requires N, 17·4%).

No trace of acidic material was obtained from the oxidation.

6-*Methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (XI).—A solution of 3-methylocta-4 : 6-dien-1-yn-3-ol (3·0 g.) and a trace of quinol in ether (20 c.c.) was shaken with dilute sulphuric acid (200 c.c.; 1% w/v) for 5 hours. Isolation of the product in the usual way gave the rearranged *carbinol* (2·75 g.), b. p. 63°/0·1 mm., n_D^{19} 1·5361 (Found : C, 79·5; H, 8·95. $C_9H_{12}O$ requires C, 79·4; H, 8·9%). Light absorption : see Table.

6-*Methyloctan*-2-*one*.—The above carbinol (2·2 g.) in acetone (20 c.c.) was shaken in hydrogen in the presence of platinic oxide until absorption was complete (1490 c.c. of hydrogen absorbed at 21°/770 mm., equivalent to 3·8 double bonds). The catalyst was removed and the saturated carbinol was oxidised with chromic acid, in the manner described above, giving 6-methyloctan-2-one (1·4 g.), b. p. 80°/20 mm., n_D^{21} 1·4220. The semicarbazone crystallised from aqueous methanol in plates, m. p. 126—128°, undepressed on admixture with an authentic specimen. The 2 : 4-dinitrophenylhydrazone crystallised from aqueous methanol in plates, m. p. 61—62°, undepressed on admixture with the specimen described above.

3-*Methylpenta*-1 : 4-*dien*-3-*ol* (XIII).—A solution of 3-methylpent-4-en-1-yn-3-ol (10 g.) (Cymerman, Heilbron, and Jones, *J.*, 1945, 90) in methanol (30 c.c.) was shaken in hydrogen in the presence of a palladium–charcoal catalyst (1 g.; 2% of Pd) until 2410 c.c. (20°/757 mm.) of gas had been absorbed (equivalent to 1 molar proportion). After removal of the catalyst, the methanol solution was diluted with water, and the product isolated with ether in the usual manner. Distillation gave 3-*methylpenta*-1 : 4-*dien*-3-*ol* (6 g.), b. p. 68—72°/120 mm., n_D^{20} 1·4400 (Found : C, 73·4; H, 10·2. $C_8H_{10}O$ requires C, 73·4; H, 10·25%).

3-*Methylpenta*-2 : 4-*dien*-1-*ol* (XIV).—(*a*) A mixture of the above carbinol (5·7 g.), dilute sulphuric acid (360 c.c.; 1% w/v), and a trace of quinol was shaken at 20° for 4 hours. Isolation of the product with ether and distillation gave 3-*methylpenta*-2 : 4-*dien*-1-*ol* (1·5 g.), b. p. 106°/80 mm., n_D^{19} 1·4942 (Found : C, 72·95; H, 10·6. $C_8H_{10}O$ requires C, 73·4; H, 10·25%). Light absorption : see Table.

A solution of the carbinol (0·5 g.) and maleic anhydride (0·5 g.) in benzene (5 c.c.) was allowed to stand at 20° overnight. The solid which separated was recrystallised from water, giving 4-*methyl*-3-*hydroxymethyl*cyclo*hex*-4-*ene*-1 : 2-*dicarboxylic acid* 2→ω-*lactone* (XIX) (0·5 g.) as needles, m. p. 182—183° (Found : C, 60·9; H, 6·1. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·15%).

(*b*) A solution of 3-methylpent-2-en-4-yn-1-ol (10 g.) (*idem*, *loc. cit.*) in methyl acetate (30 c.c.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (1 g.; 6% of Pd) until 2509 c.c. of gas had been absorbed at 20°/760 mm., whereafter the reaction was interrupted. Removal of the catalyst and solvent, and distillation of the residue, gave 3-methylpenta-2 : 4-dien-1-ol (6 g.), b. p. 68—71°/15 mm., n_D^{20} 1·4840—1·4920 (the product was collected in several fractions which differed but slightly in their light-absorption intensities). The maleic anhydride adduct, prepared as described above, had m. p. 182—183°, undepressed on admixture with a specimen from (*a*).

6-*Methylocta*-3 : 5 : 7-*trien*-2-*one* (II).—(*a*) A mixture of 6-methylocta-3 : 5 : 7-trien-2-ol (45 g.), aluminium *tert.*-butoxide (140 g.), dry benzene (3 l.), and dry acetone (1·4 l.) was heated under reflux for 24 hours. Ice and dilute sulphuric acid (10% w/v) were added, and the benzene layer separated and washed with water, sodium hydrogen carbonate solution, and again with water. The dried ($MgSO_4$) benzene solution was evaporated under reduced pressure, the temperature being kept below 50°, and the residue distilled rapidly in small batches, giving 6-*methylocta*-3 : 5 : 7-*trien*-2-*one* (30 g.) as a pale yellow unstable liquid, b. p. 79—80°/0·9 mm., n_D^{25} 1·5796—1·5880 (Found : C, 79·05; H, 9·15. $C_9H_{12}O$ requires C, 79·35; H, 9·15%). Light absorption : Maximum, 3080 A.; ε, 30,000. Each batch was collected in several fractions which showed only slight differences in light-absorption intensity. (No trace of unchanged carbinol could be detected, but a considerable amount of a transparent polymer was also formed.) The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark red needles, m. p. 203° (Found : N, 18·0. $C_{15}H_{16}O_4N_4$ requires N, 17·7%). Light absorption in chloroform (main band only) : Maximum, 4000 A.; ε, 43,000. The *semicarbazone* crystallised from methanol in plates

which decomposed when heated (Found: N, 21·65. $C_{16}H_{18}ON_2$ requires N, 21·75%). Light absorption: Maxima, 2800, 3160, and 3290 A.; ε, 27,000, 52,000, and 40,500, respectively.

In small-scale experiments, the ketone (II) was obtained in yields up to 80%.

(*b*) A solution of 6-methylocta-3 : 5 : 7-trien-2-ol (4 g.) and aluminium phenoxide (9 g.) in acetone (60 c.c.) and benzene (130 c.c.) was heated under reflux for 24 hours. After cooling, the solution was poured into dilute sulphuric acid (10% w/v), and the benzene layer was separated and washed with dilute sodium hydroxide solution (10% w/v) and water. The benzene solution was dried and evaporated under reduced pressure. Distillation of the residue gave 6-methylocta-3 : 5 : 7-trien-2-one (2·4 g.), b. p. 51°/0·1 mm., n_D^{19} 1·5893—1·5991. Light absorption: Maximum, 3080 A.; ε, 31,500. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in dark red needles, m. p. 203°, undepressed on admixture with a specimen from (*a*).

(*c*) A solution of 3-methylpenta-2 : 4-dien-1-ol (9·2 g.) and aluminium *tert.*-butoxide (27 g.) in acetone (270 c.c.) and benzene (675 c.c.) was heated under reflux for 36 hours. Isolation of the product in the usual manner and distillation gave 6-methylocta-3 : 5 : 7-trien-2-one (3·8 g.), b. p. 49—54°/10^{-2} mm., n_D^{19} 1·5805—1·5890. Light absorption: Maximum, 3080 A.; ε, 30,000. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in dark red needles, m. p. 204—205°, undepressed on admixture with a specimen from (*a*).

(*d*) A solution of 6-methylocta-3 : 5-dien-7-yn-2-ol (4·1 g.) in methyl acetate (30 c.c.) was shaken in an atmosphere of hydrogen in the presence of a palladium–calcium carbonate catalyst (0·4 g.; 0·3% of Pd) until 740 c.c. of hydrogen had been absorbed at 18°/754 mm., equivalent to 1 molar proportion. The reaction was interrupted and the catalyst and solvent were removed. Distillation of the residue gave the crude triene carbinol (2·9 g.), b. p. 60—65°/0·1 mm., n_D^{21} 1·5329—1·5469, which was dissolved in acetone (90 c.c.) and added to a solution of aluminium *tert.*-butoxide (9·0 g.) in benzene (200 c.c.). The solution was boiled under reflux for 24 hours, and the product isolated in the usual way, giving the crude ketone (1·7 g.), b. p. 52—55°/0·1 mm., n_D^{17} 1·5752—1·5792. Light absorption: Maximum, 3050 A.; $E_{1\text{ cm.}}^{1\%}$, 1840—2100. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in dark red needles, m. p. 203°, undepressed on admixture with a specimen from (*a*).

(*e*) (With Marc Julia.) A solution of 3-methylpenta-2 : 4-dien-1-al (1·35 g.; crude, b. p. 54—61°/20 mm., n_D^{22} 1·4883. Light absorption: Maxima, 2520 and 2590 A.; $E_{1\text{ cm.}}^{1\%}$, 1600 and 1580, respectively. Inflexion, 2420 A.; $E_{1\text{ cm.}}^{1\%}$, 1300), prepared from 1-ethoxy-3-methylpent-4-en-1-yn-3-ol (4·1 g.) by the method of Heilbron, Jones, Julia, and Weedon (*loc. cit.*), and aluminium *tert.*-butoxide (6 g.) in acetone (40 c.c.) and benzene (100 c.c.) was boiled under reflux for 12 hours. Isolation of the product in the usual manner gave an oil (0·5 g.), b. p. *ca.* 50°/10^{-2} mm., n_D^{18} 1·5561. Light absorption: Maximum, 3050 A., $E_{1\text{ cm.}}^{1\%}$, 1140, indicating a content of *ca.* 50% of the ketone (II). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark red needles, m. p. 174—176°, and is isomeric with the derivative described above (Found: C, 56·45; H, 5·4; N, 17·65. $C_{15}H_{16}O_4N_4$ requires C, 56·8; H, 5·1; N, 17·7%). Light absorption in chloroform (main band only): Maximum, 4050 A.; ε, 35,000.

The condensation was also effected by adding a solution of sodium hydroxide (0·6 g.) in aqueous alcohol (4 c.c.; 50% w/v) to a cooled solution of the crude aldehyde (1·8 g.) in acetone (8 c.c.). After 15 minutes at 20°, the resulting dark brown mixture was acidified with dilute sulphuric acid (10% w/v), and the crude ketone (1·5 g.), b. p. *ca.* 40°/10^{-3} mm., isolated in the usual way. Light absorption: Maximum, 3050 A.; $E_{1\text{ cm.}}^{1\%}$, 1000. The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in needles, m. p. 204°, undepressed on admixture with a specimen from (*a*).

6-*Methyloctan*-2-*one*.—A solution of 6-methylocta-3 : 5 : 7-trien-2-one (0·5 g.) in methyl acetate (10 c.c.) was shaken in hydrogen in the presence of platinic oxide until absorption was complete (250 c.c. of hydrogen absorbed at 13°/772 mm., equivalent to 2·9 double bonds). Removal of catalyst and solvent gave 6-methyloctan-2-one (0·45 g.), n_D^{18} 1·4225. The semicarbazone crystallised from aqueous methanol in plates, m. p. 128°, undepressed on admixture with the specimen described above.

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434. *Preparation of β-Phenoxypropionic Acids by the Reaction of Phenols with Ethyl Acrylate.*

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A number of β-halogenophenoxypropionic acids is prepared by the condensation of halogenophenols and ethyl acrylate in presence of sodium and direct hydrolysis of the reaction mixture with cold aqueous alkali.

Recently Rehberg, Dixon, and Fisher reported (*J. Amer. Chem. Soc.*, 1947, **69**, 2966; 1946, **68**, 544) that under mild, alkaline, anhydrous conditions primary and secondary, but not tertiary, aliphatic alcohols readily add to the olefinic linkage of alkyl acrylates, giving good yields

of β-alkoxypropionates. In the present paper the condensation of phenol and halogenophenols with ethyl acrylate is used to prepare the corresponding β-phenoxy- and β-halogenophenoxypropionic acids, some of which have previously been synthesised by other methods.

$$CH_2{:}CH{\cdot}CO_2Et + ROH \longrightarrow RO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$$

Thus β-phenoxypropionic acid has been prepared by treating sodium or potassium phenoxide with a β-halogenopropionic acid (Bischoff, *Ber.*, 1900, **33**, 924; Arndt and Källner, *ibid.*, 1924, **57**, 202), or by oxidising 3-phenoxypropan-1-ol (Powell, *J. Amer. Chem. Soc.*, 1923, **45**, 2708); these methods have been applied in the preparation of substituted phenoxypropionic acids, *e.g.*, by Chakravarti and Dutta (*J. Indian Chem. Soc.*, 1939, **16**, 639) and by Synerholm and Zimmermann (*Contrib. Boyce Thompson Inst.*, 1947, **14**, 369), respectively. β-*p*-Chlorophenoxypropionic acid has also been prepared by chlorinating β-phenoxypropionic acid (Haskelberg, *J. Org. Chem.*, 1947, **12**, 426). After the present work had been completed, Gresham, Jansen, Shaver, Bankert, Beears, and Prendergast (*J. Amer. Chem. Soc.*, 1949, **71**, 661; cf. Gresham and Shaver, U.S.P. 2,449,991; *Chem. Abs.*, 1949, **43**, 1053) reported the preparation of a number of substituted β-phenoxypropionic acids by interaction of β-propionolactone with phenols and their salts. As far as could be ascertained, the only references to the direct condensation of phenol and an ester of acrylic acid are D.R.-P. 670,357 (I.G. Farbenind. A.-G. and H. Ufer) and the equivalent F.P. 833,734, which claim the addition of aromatic hydroxy-compounds to derivatives of acrylic acid.

It has now been found that phenol and substituted phenols add to the olefinic linkage of ethyl acrylate under more drastic conditions than those required for aliphatic alcohols. Temperatures between 95° and 110° were generally satisfactory. As only small samples of the substituted β-phenoxypropionic acids prepared were required for other purposes the reactions were carried out under standard, not necessarily optimal, conditions. Considerable improvements in yields could no doubt be effected, as most of the unchanged acrylate and phenol was recovered.

The β-phenoxypropionic esters which were the primary reaction products were isolated in the first experiments and found to be extremely readily hydrolysed by aqueous alkali; in working up the subsequent reaction mixtures it was convenient, therefore, to add concentrated aqueous sodium hydroxide to convert the esters, at least in part, into the corresponding acids which could thus be obtained directly. The acids were characterised as the amides; the *ethyl* esters were low-melting solids, although ethyl β-phenoxypropionate, the only one previously prepared, was described as an oil.

Experimental.

All m. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss of Oxford.

β-Phenoxypropionic Acid.—Metallic sodium (0·5 g.) was dissolved in "AnalaR" phenol (47 g.), m. p. 41°, and ethyl acrylate (50 g.), b. p. 99°, n_D^{18} 1·4046 (purity, ~95%), containing quinol (0·1 g.) was added. The mixture was heated at 95—110° for 40 hours; when cool it was diluted with water (100 ml.) containing acetic acid (0·5 ml.). Ether-extraction, drying (Na_2SO_4), and removal of the ether and unchanged ethyl acrylate under reduced pressure afforded a viscous oil which was separated by fractional distillation into unchanged phenol (23 g.), b. p. 75°/11 mm., which solidified on seeding, and ethyl β-phenoxypropionate (48 g.), b. p. 142°/11 mm., n_D^{18} 1·5007, which solidified when kept and then crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 24° (sap. val., 291. Calc. for $C_{11}H_{14}O_3$: sap. val., 289) (Koelsch, *J. Amer. Chem. Soc.*, 1930, **52**, 2430, gives b. p. 175—177°/50 mm., and n_D^{25} 1·5055). Hydrolysis of the ester (1 g.) with a N-solution of potassium hydroxide in 50% aqueous ethanol (25 ml.) at room temperature was complete in about 5 minutes and gave β-phenoxypropionic acid (0·7 g.) which crystallised from aqueous methanol in leaflets, m. p. 97—98° (equiv., by titration with 0·05N-potassium hydroxide, 169. Calc. for $C_9H_{10}O_3$, 166) (Powell, *loc. cit.*, gives m. p. 98°, Koelsch, *loc. cit.*, m. p. 96—97°, and Gresham *et al.*, *loc. cit.*, m. p. 94—95°). Treating the acid with excess of thionyl chloride in the cold and pouring into concentrated aqueous ammonia at 0° gave β-phenoxypropionamide, which crystallised from aqueous methanol in needles, m. p. 119° (Powell, *loc. cit.*, gives m. p. 119°).

β-p-Chlorophenoxypropionic Acid.—(*a*) Use of *p*-chlorophenol (64·5 g.), m. p. 40—41°, instead of phenol in the above reaction led to *ethyl β-p-chlorophenoxypropionate* (44 g.), b. p. 90°/0·2 mm., n_D^{17} 1·5134, which solidified on standing and then crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 34—35° (Found: C, 58·2; H, 5·95; Cl, 15·55. $C_{11}H_{13}O_3Cl$ requires C, 57·8; H, 5·7; Cl, 15·5%). The ester on hydrolysis as before gave β-*p*-chlorophenoxypropionic acid, which crystallised from aqueous methanol in fine plates, which melted sharply at 135·5° (Chakravarti and Dutta, *loc. cit.*, give m. p. 138—139°, Haskelberg, *loc. cit.*, m. p. 139°, and Gresham *et al.*, *loc. cit.*, m. p. 134—135°).

(*b*) This acid (38 g.) was also obtained by condensing *p*-chlorophenol and ethyl acrylate over sodium as above, diluting the reaction mixture with ether (150 ml.), shaking (5 minutes) thrice with 25% aqueous sodium hydroxide (50 ml. each time), and acidifying the aqueous layers with concentrated hydrochloric acid. The viscous oil so obtained contained the desired acid and unchanged *p*-chlorophenol; it was dissolved in ether and extracted with saturated aqueous sodium hydrogen carbonate; the acid (38 g.) was precipitated on acidification of the aqueous layer. *β-p-Chlorophenoxypropionamide*,

prepared from the acid in the usual manner, crystallised from 2N-ammonia, containing a little methanol, in needles, m. p. 136—137° (Found : C, 53·8; H, 5·15; N, 6·7. $C_9H_{10}O_3NCl$ requires C, 54·15; H, 5·05; N, 7·0%). The original ethereal solution remaining after extraction with sodium hydroxide was evaporated and gave ethyl *β-p*-chlorophenoxypropionate (6 g.) which had not been hydrolysed and was identical with the ester obtained by method (*a*).

β-o-Chlorophenoxypropionic Acid.—Reaction of *o*-chlorophenol (64 g.), b. p. 92°/55 mm., n_D^{20} 1·5580, with ethyl acrylate (50 g.) by method (*b*) gave *ethyl β-o-chlorophenoxypropionate* (12 g.), b. p. 87°/0·1 mm., n_D^{20} 1·5130 (Found : C, 57·95; H, 5·95. $C_{11}H_{13}O_3Cl$ requires C, 57·8; H, 5·7%), which crystallised from light petroleum, cooled in acetone containing solid carbon dioxide, in needles, m. p. 2·5—4·5°, and *β-o*-chlorophenoxypropionic acid (7·5 g.) which crystallised from aqueous methanol in needles, m. p. 111° (Chakravarti and Dutta, *loc. cit.*, give m. p. 108—109°, and Gresham *et al.*, *loc. cit.*, m. p. 112—113°). The acid was characterised as *β-o-chlorophenoxypropionamide*, which crystallised from 2N-ammonia containing a little methanol in leaflets, m. p. 90° (Found : C, 53·75; H, 5·2; N, 6·55. $C_9H_{10}O_3NCl$ requires C, 54·15; H, 5·05; N, 7·0%).

β-2 : 4-Dichlorophenoxypropionic Acid.—By method (*b*) 2 : 4-dichlorophenol (80 g.), m. p. 45°, and ethyl acrylate (50 g.) gave *ethyl β-2 : 4-dichlorophenoxypropionate* (8 g.), b. p. 115°/0·1 mm., n_D^{20} 1·5149 (Found : C, 50·55; H, 4·85. $C_{11}H_{12}O_3Cl_2$ requires C, 50·2; H, 4·6%), which crystallised from light petroleum in needles, m. p. 16—17°, and *β-2 : 4*-dichlorophenoxypropionic acid (25 g.) which crystallised from aqueous methanol in needles, m. p. 92—93° (Synerholm and Zimmermann, *loc. cit.*, give m. p. 93°, and Gresham *et al.*, *loc. cit.*, m. p. 91—92°). The acid was converted into the amide which on slow crystallisation from aqueous methanol gave leaflets, m. p. 104° (Synerholm and Zimmermann, *loc. cit.*, give m. p. 104°).

β-4-Chloro-2-methylphenoxypropionic Acid.—5-Chloro-*o*-cresol (42 g.), m. p. 48° (obtained from *o*-cresol and sulphuryl chloride by the method of Sah and Anderson, *J. Amer. Chem. Soc.*, 1941, **63**, 3164), with ethyl acrylate (25 g.) [method (*b*)] gave *ethyl β-4-chloro-2-methylphenoxypropionate* (10 g.), b. p. 84°/0·3 mm., n_D^{20} 1·5102, which solidified on standing and then crystallised from light petroleum in needles, m. p. 22·5—23·5° (Found : C, 59·75; H, 6·1. $C_{12}H_{15}O_3Cl$ requires C, 59·4; H, 6·25%), and *β-4-chloro-2-methylphenoxypropionic acid* (22 g.) which crystallised from aqueous methanol in needles, m. p. 104° (Found : C, 56·1; H, 5·4. $C_{10}H_{11}O_3Cl$ requires C, 55·95; H, 5·2%). The *amide* crystallised from aqueous methanol in needles, m. p. 94° (Found : C, 56·5; H, 5·9; N, 6·75. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·65; N, 6·55%).

β-4-Chloro-3-methylphenoxypropionic Acid.—6-Chloro-*m*-cresol (72 g.), m. p. 66° (obtained from *m*-cresol and sulphuryl chloride using the procedure of Sah and Anderson, *loc. cit.*), with ethyl acrylate (50 g.) [method (*b*)] gave *ethyl β-4-chloro-3-methylphenoxypropionate* (10 g.), b. p. 96·5—97°/0·1 mm., n_D^{20} 1·5144, which solidified on storage, and on crystallisation from light petroleum had m. p. 31—32° (Found : C, 59·65; H, 6·3; Cl, 14·9. $C_{12}H_{15}O_3Cl$ requires C, 59·4; H, 6·25; Cl, 14·6%), and *β-4-chloro-3-methylphenoxypropionic acid* (33·5 g.) which crystallised from aqueous methanol in needles, m. p. 142° (Found : C, 56·2; H, 5·3. $C_{10}H_{11}O_3Cl$ requires C, 55·95; H, 5·2%). The derived *amide* crystallised from aqueous methanol in leaflets, m. p. 113° (Found : C, 56·3; H, 5·75; N, 6·7. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·65; N, 6·55%).

β-2-Chloro-4-methylphenoxypropionic Acid.—3-Chloro-*p*-cresol (72 g.), b. p. 195—197°, n_D^{20} 1·5531 (prepared from *p*-cresol by the method of Sah and Anderson, *loc. cit.*, who give b. p. 195—197°, n_D^{27} 1·5200), and ethyl acrylate (50 g.) [method (*b*)] gave *ethyl β-2-chloro-4-methylphenoxypropionate* (26·5 g.), b. p. 95°/0·1 mm., n_D^{20} 1·5130, which crystallised from light petroleum (cooled in acetone containing solid carbon dioxide) in needles, m. p. 14—14·5° (Found : C, 59·7; H, 6·25; Cl, 14·3. $C_{12}H_{15}O_3Cl$ requires C, 59·4; H, 6·25; Cl, 14·6%), and *β-2-chloro-4-methylphenoxypropionic acid* (20 g.) which crystallised from aqueous methanol in needles, m. p. 129° (Found : C, 55·9; H, 5·3. $C_{10}H_{11}O_3Cl$ requires C, 55·95; H, 5·2%). The *amide* crystallised from 2N-ammonia, containing methanol, in leaflets, m. p. 112° (Found : C, 56·15; H, 5·75; N, 6·8. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·65; N, 6·55%).

β-p-Bromophenoxypropionic Acid.—*p*-Bromophenol (86 g.), m. p. 63°, and ethyl acrylate (50 g.) [method (*b*)] gave *ethyl β-p-bromophenoxypropionate* (5 g.), b. p. 134°/0·2 mm., n_D^{20} 1·5308, which solidified when kept and after crystallisation from light petroleum had m. p. 44° (Found : C, 48·65; H, 4·9. $C_{11}H_{13}O_3Br$ requires C, 48·4; H, 4·8%), and *β-p*-bromophenoxypropionic acid (25 g.) which crystallised from methanol in plates, m. p. 144—145° (Gresham *et al.*, *loc. cit.*, give m. p. 142—143°) (Found : C, 44·6; H, 3·4; Br, 32·0. Calc. for $C_9H_9O_3Br$: C, 44·1; H, 3·7; Br, 32·6%). The *amide* crystallised from aqueous methanol in needles, m. p. 136° (Found : C, 44·8; H, 4·25; N, 5·4. $C_9H_{10}O_2NBr$ requires C, 44·3; H, 4·15; N, 5·7%).

β-o-Bromophenoxypropionic Acid.—*o*-Bromophenol (24 g.), n_D^{20} 1·5844, and ethyl acrylate (14 g.) [method (*b*)] gave *ethyl β-o-bromophenoxypropionate* (5 g.), b. p. 108°/0·1 mm., n_D^{20} 1·5291, which crystallised from light petroleum (cooled in acetone containing solid carbon dioxide) in needles, m. p. 11—12° (Found : C, 49·0; H, 5·0; Br, 29·4. $C_{11}H_{13}O_3Br$ requires C, 48·4; H, 4·8; Br, 29·25%), and *β-o*-bromophenoxypropionic acid, plates, m. p. 109·5—110°, from aqueous methanol (Gresham *et al.*, *loc. cit.*, give m. p. 109—110°) (Found : C, 44·5; H, 3·9. Calc. for $C_9H_9O_3Br$: C, 44·1; H, 3·7%). The *amide* crystallised from methanol–2N-aqueous ammonia in needles, m. p. 117° (Found : C, 44·9; H, 4·25; N, 5·55. $C_9H_{10}O_2NBr$ requires C, 44·3; H, 4·15; N, 5·7%).

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435. *Lanosterol. Part VIII. The Action of Perbenzoic Acid on Derivatives of Lanosterol.*

By M. J. Birchenough and J. F. McGhie.

α-Dihydrolanosteryl acetate absorbed one atom of oxygen per molecule when treated with an excess of perbenzoic acid, and the final product was the doubly unsaturated α-dihydroagnosteryl acetate. The results obtained in perbenzoic acid titrations of a number of lanosterol derivatives are recorded; the number of atoms of oxygen absorbed per molecule approximated in each case to a whole number, but in the agnosterol series was always one less than the number of double bonds present.

Conflicting results have been reported by earlier workers investigating the action of perbenzoic acid on "lanosterol" (Windaus, *Z. physiol. Chem.*, 1930, **190**, 59; Dorée and Garratt, *J. Soc. Chem. Ind.*, 1933, **52**, 360T; Dorée and Petrow, *J.*, 1936, 1561). Recently Ruzicka (*Helv. Chim. Acta*, 1945, **28**, 759) has shown that the "lanosterol" of previous workers was, in fact, a mixture of lanosterol $C_{30}H_{50}O$ and dihydrolanosterol $C_{30}H_{52}O$, which on catalytic hydrogenation yields pure dihydrolanosterol (Marker, *J. Amer. Chem. Soc.*, 1937, **59**, 1368). Some disagreement exists, however, in the values reported for the per-acid titration of dihydrolanosterol. Wieland *et al.* (*Annalen*, 1937, **529**, 68) working on cryptosterol, which subsequent work (Ruzicka *et al.*, *Helv. Chim. Acta*, 1945, **28**, 759; McGhie, Thesis, London, 1947) has shown to be identical with lanosterol, found that dihydrocryptosteryl acetate absorbed one atom of oxygen to give an "oxide," m. p. 142°, $[\alpha]_D^{20}$ +1·7°. On the other hand, Muhr (Thesis, Zurich, 1945) found that dihydrolanosteryl acetate did not absorb oxygen from monoperphthalic acid at −10°. These conflicting results made it seem desirable to reinvestigate the problem, and we now record our findings.

Perbenzoic acid reacts with dihydrolanosteryl acetate to give a labile intermediate, m. p. 142°, $[\alpha]_D^{20}$ +28·5°, provisionally assumed to be an "oxide." This "oxide" on treatment with sulphuric acid in glacial acetic acid, or on long heating with acetic anhydride, gives a product m. p. 167—168°, $[\alpha]_D^{20}$ +86·0°, which is also obtained from the mother-liquors from the perbenzoic oxidation of α-dihydrolanosteryl acetate.

The intermediate is so labile that ready conversion into the diene takes place when recrystallisation is attempted. This is shown by the progressive increase in the intensity of the ultra-violet light absorption at 243 mμ. and by the approach towards the value for the specific rotation of α-dihydroagnosteryl acetate. Thus, it has not been possible to obtain the so-called "oxide" in the pure state for further investigation; a similar example was observed by Windaus and Luttringhaus (*Annalen*, 1930, **481**, 119) in the case of α-ergostenyl acetate.

The compound, m. p. 167—168°, $[\alpha]_D^{20}$ +86·0°, has an ultra-violet absorption spectrum identical with that of α-dihydroagnosteryl acetate, and a close comparison of the two, and of their derivatives (see Table I), established the identity beyond reasonable doubt.

Table I.

Derivative.	α-Dihydroagnosteryl acetate.* M. p.	$[\alpha]_D^{20}$.	Perbenzoic acid oxidn. product. M. p.	$[\alpha]_D^{20}$.
Acetate	168—169°	+87·8°	167—168°	+86·0°
Alcohol	157—158	+67·5	157	+65·4
Ketone	131—132	+47·7	128—129	+44·5
Ultra-violet absorption of acetate.	$\lambda_{max.}$ = 243 mμ. ($E^{1\%}_{1\,cm.}$ = 360); $\lambda_{max.}$ = 251 mμ. ($E^{1\%}_{1\,cm.}$ = 225);		$\lambda_{max.}$ = 243 mμ. ($E^{1\%}_{1\,cm.}$ = 350). $\lambda_{max.}$ = 251 mμ. ($E^{1\%}_{1\,cm.}$ = 240).	

* Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 204.

The introduction of a second olefinic linkage into α-dihydrolanosteryl acetate by means of perbenzoic acid is similar to the conversion of α-ergostenol into dehydroergostenol by perbenzoic acid through the intermediate oxide (Windaus and Luttringhaus, *loc. cit.*; Morrison and Simpson, *J.*, 1932, 1710). As in the case of α-dihydrolanosteryl acetate which is dehydrogenated to α-dihydroagnosteryl acetate by selenium dioxide (Dorée and Bellamy, *J.*, 1941, 176), α-ergostenol yields dehydroergostenol (Callow, *J.*, 1936, 462).

The second nuclear double bond in dihydroagnosterol, like that in dihydrolanosterol, is unreactive: it cannot, for example, be catalytically hydrogenated. α-Dihydroagnosteryl acetate, although containing two double bonds, was found, under the conditions here described, to absorb only one atom of oxygen per molecule. This parallel between lanosterol and agnosterol

compounds is maintained in the hydrocarbons obtained by dehydration of the alcohols with phosphorus oxychloride and with phosphorus pentachloride, yielding two series of isomeric hydrocarbons (Dorée, McGhie, and Kurzer, *J.*, 1947, 1467).

The values obtained for the titration of these derivatives with perbenzoic acid are summarised in Table II. In all the cases where dehydrogenation by perbenzoic acid has taken place, the

TABLE II.

Derivative.	Atoms of oxygen absorbed per molecule. 30 mins.	5 hrs.	24 hrs.	48 hrs.	7 days.
α-Dihydrolanosteryl acetate	0·7	1·0	1·0	1·0	1·1
Lanostadiene	—	2·0	2·1	2·1	2·1
*iso*Lanostadiene	1·7	1·9	2·0	2·0	2·0
α-Dihydroagnosteryl acetate	1·0	1·0	1·2	1·2	1·2
Lanostatriene	—	—	2·2	2·2	2·2
*iso*Lanostatriene	—	—	2·0	2·1	2·1

parent compound has contained an " inert " double bond; thus, for this type of compound, dehydrogenation rather than formation of a stable oxide may be the predominant reaction. It was suggested in an earlier communication (Dorée, McGhie, and Kurzer, this vol., p. 570) that the dehydrogenation of dihydrolanosteryl acetate to dihydroagnosteryl acetate by selenium dioxide and *N*-bromosuccinimide might well be represented by the scheme outlined in the partial formulæ :

$$>C{:}\dot{C}{\cdot}CH{\cdot}CH< \longrightarrow >C{:}\dot{C}{\cdot}\dot{C}X{\cdot}CH< \longrightarrow >C{:}\dot{C}{\cdot}\dot{C}{:}C<,$$

where X = OH or Br. The isolation of the same product after reaction with perbenzoic acid makes it probable that this reaction follows a similar course, the isolation of the labile intermediate being attributable to the extremely mild conditions of the experiment.

The results here reported afford a further example of non-correspondence between the number of double linkages known to be present and the number indicated by titration with perbenzoic acid. They add emphasis to Ruzicka's views (*Helv. Chim. Acta*, 1932, **15**, 1294) on the need for caution in interpreting the results obtained with this reagent.

EXPERIMENTAL.

All m. p.s are uncorrected. Analyses and rotations by Drs. Weiler and Strauss, Oxford. All rotations in chloroform at 20°.

Titrations with Perbenzoic Acid.—General procedure. To a solution of the substance in chloroform at 0°, a 50% excess of perbenzoic acid in chloroform was added, the mixture being kept at 0° throughout. Aliquot portions were withdrawn at intervals and treated with an excess of potassium iodide, the solution was acidified, and the liberated iodine titrated with standard sodium thiosulphate solution. The results are recorded in Table II.

Dehydrogenation of α-Dihydrolanosteryl Acetate.—To a solution of α-dihydrolanosteryl acetate (5 g.) in chloroform (20 ml.) was added a solution of perbenzoic acid in chloroform (equivalent to 0·28 g. of active oxygen). After 40 hours the excess of oxidising agent was decomposed by potassium iodide, the mixture acidified, and the liberated iodine removed by shaking with 0·1N-thiosulphate. The chloroform layer was separated and washed twice with 2N-sodium hydroxide and then twice with water. The solution was dried (Na_2SO_4), the chloroform removed under reduced pressure, and the residue crystallised from chloroform–methanol to give lustrous plates (4 g.), m. p. 142°, $[\alpha]_D^{20}$ +28·5° (*c*, 0·97) (Found: C, 79·4; H, 10·7. Calc. for $C_{32}H_{54}O_2$: C, 78·9; H, 11·2%). This product contains approx. 20% of α-dihydroagnosteryl acetate as calculated from the ultra-violet absorption data. The mother-liquors yielded 0·75 g. of impure α-dihydroagnosteryl acetate, m. p. 162°.

Conversion of the " Oxide," m. p. 142°, into α-Dihydroagnosteryl Acetate.—A solution of 1 g. of the " oxide " in glacial acetic acid (20 ml.) was treated at the boiling point with 3 drops of concentrated sulphuric acid. On cooling, a product (0·8 g.), m. p. 167—168°, crystallised (Found: C, 81·9; H, 10·9. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%); it showed no depression in m. p. on admixture with α-dihydroagnosteryl acetate, $[\alpha]_D^{20}$ +86·0° (*c*, 1·0). Hydrolysis with 5% alcoholic potash gave the alcohol, m. p. 157° (Found: C, 84·25; H, 11·6. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%), $[\alpha]_D^{20}$ +65·4° (*c*, 0·70). Oxidation of the alcohol by Kiliani's chromic acid mixture gave the ketone, m. p. 128—129° (Found: C, 84·6; H, 11·20. Calc. for $C_{30}H_{48}O$: C, 84·8: H, 11·4%), $[\alpha]_D^{20}$ +44·5° (*c*, 1·0).

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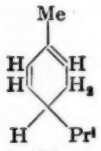
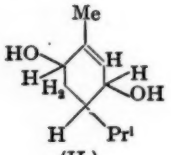
436. *Autoxidation of α-Phellandrene.*

By A. Blumann and L. Ryder.

Autoxidation of α-phellandrene produces, besides the known *p*-menth-1-ene-3 : 6-diol, m. p. 164—165°, a mixture including an isomeric *diol*, m. p. 54°. These substances are shown to be *trans*- and *cis*-forms, respectively.

The formation of a substance, $C_{10}H_{18}O_2$, m. p. 164—165°, from French bitter fennel oil was observed by Schimmel & Co. (Semi-annual Report, April 1901). Clover (*Philippine J. Sci.*, 1907, 1; *Amer. Chem. J.*, 1908, **39**, 640), who found the substance in oil of elemi, proved that it was derived from α-phellandrene (I). After further investigations (Schmidt, Thesis, Göttingen, 1925, pp. 39, 77; Faber, Thesis, Göttingen, 1927, p. 28; Mladenovic, *Monatsh.*, 1934, **64**, 177), Bodendorf (*Arch. Pharm.*, 1933, **271**, 9) suggested that it was a *p*-menth-1-ene-3 : 6-diol, a constitution which was proved by Dupont (*Bull. Ind. Chim. Belge*, 1940, 10) and is now confirmed by the action of acids on the diol.


(I.)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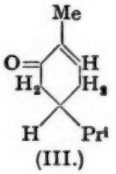
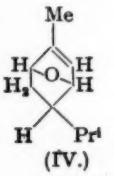

(III.)

Concentrated acids convert the diol into carvotanacetone (III) which, at first sight, might be held to originate from an α-glycol (cf. Ralph, *Proc. Roy. Soc. N.S.W.*, 1947, **80**, 210; *Aust. J. Sci.*, 1948, Dec., 98). However, with very dilute sulphuric acid, the diol loses water to form an *oxide* (IV), which readily yields carvotanacetone (and *p*-cymene) in presence of concentrated acid. The same oxide is obtained from the oils remaining after removal of the diol, m. p. 164—165°, but then has a lower optical rotation.

Autoxidation of commercial (−)-α-phellandrene (from the oil of *Eucalyptus dives*) readily gives the same diol, m. p. 164—165°, but in small and variable yield, together with a much larger amount of a viscous mixture of isomers, whence an isomeric *diol*, m. p. 54°, can be isolated. Both compounds are also obtained by leaching the high-boiling (piperitone) fractions of *E. dives* oil with water.

The substances, m. p. 164—165° and 27°, are respectively *trans*- and *cis*-*p*-menth-1-ene-3 : 6-diol (cf. terpin hydrate and the glycol, m. p. 60°, from autoxidised limonene; Blumann and Zeitschel, *Ber.*, 1914, **47**, 2623; H. Schmidt, private communication; cf. von Baeyer, *Ber.*, 1896, **29**, 1198). The compound, m. p. 164—165°, has the higher b. p., is sparingly soluble in water, distils unchanged at atmospheric pressure (whereas the isomer decomposes), and gives, with acetic anhydride, a quantitative yield of a crystalline *diacetate* (the yield from the isomer is lower owing to decomposition). Thus, the diols behave relatively in the same way as do *neo*menthol and menthol (Zeitschel and Schmidt, *Ber.*, 1926, **59**, 2298).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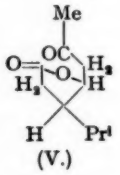
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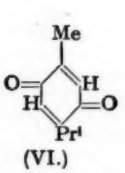

(VI.)

Both diols are readily hydrogenated in the presence of a nickel catalyst under mild conditions, but noble-metal catalysts are apparently unsuitable [cf. Bodendorf (*loc. cit.*) and Mladenovic (*loc. cit.*); cf. also the hydrogenation of α-terpineol (Zeitschel and Schmidt, *Ber.*, 1927, **60**, 1372)]. The saturated *cis*-form loses water readily when heated with 10% sulphuric acid, but the corresponding *trans*-form can be recrystallised unchanged from this medium.

The unsaturated diols and the saturated *cis*-diol have no odour or taste; the saturated *trans*-diol is also odourless, but produces on the palate and in the throat the same sensation as does pure menthol, although free from unpleasant taste.

With Beckmann's chromic acid mixture (cf. Henry and Paget, *J.*, 1928, 72) both diols yield the keto-lactone (V) and thymoquinone (VI).

Experimental.

Oxidation of α-Phellandrene.—(*a*) Oxygen was bubbled through phellandrene, α_D −118°, at 35—40° until the density was >1. To 1 kg. of the product water was added, and the mixture (which was acid) was steam-distilled after addition of magnesium carbonate (148 g.). The residue was thoroughly washed with hot water, the aqueous extracts (*X*) were combined (see below), and the oily layer was distilled, yielding fractions (i) (29 g.) b. p. 138°/25 mm., n_D^{20} 1·4820, (ii) (74 g.) b. p. 130°/5·5 mm., n_D^{20} 1·4870, (iii) (28 g.) b. p. 145°/10 mm., n_D^{20} 1·4925, (iv) (130 g.) b. p. 180°/11·5 mm., (v) (16 g.) b. p. 186°/11·5 mm., and a residue (126 g.). Fractions (iv) and (v) partly crystallised, yielding 7·5 g. of *trans-p*-menth-1-ene-3 : 6-diol; the remainder of fractions (iv) and (v) was bulked with fraction (iii) and refractionated to yield (vi) (10 g.) b. p. 105°/7 mm., α_D −13·6°, (vii) (8 g.) b. p. 134°/7 mm., α_D −16·8°, (viii) (23 g.) b. p. 135°/8 mm., α_D −15·3°, (ix) (20·5 g.) b. p. 145°/8 mm., α_D −14·5°, (x) (21 g.) b. p. 155°/8 mm., α_D −7·0°, (xi) (20 g.) b. p. 157°/8 mm., α_D +11·0°, (xii) (18 g.) b.p. 175°/8 mm., (xiii) (2 g.) b. p. 178°/8 mm., and a residue (25 g.). Fractions (vi)—(x) were combined and washed with hot water, but only 2 g. were dissolved; they were therefore washed with light petroleum, after which the bottom layer was fractionated, yielding fractions (xiv) (7·5 g.) b. p. 115°/4·5 mm., α_D −28°, (xv) (16·5 g.) b. p. 124°/3 mm., α_D −20°, (xvi) (5·5 g.) b. p. 130°/3·5 mm., α_D −18·1°, (xvii) (6·5 g.) b. p. 135°/3·5 mm., α_D +3·8°, (xviii) (2·5 g.) b. p. 142°/3·5 mm., and a residue (8 g.); fractions (xvii) and (xviii) crystallised.

The aqueous extracts (X) were concentrated *in vacuo* as far as possible and salted out. The top layer was dried at 80 mm. and extracted with 200 c.c. of benzene. The extract was filtered and, after removal of the benzene, distilled to give 10 g. of "*cis*-fraction," b. p. 125°/7 mm. to 170°/11 mm., α_D −35·8°, and a residue (19 g.).

(*b*) After 90 lb. of α-phellandrene had been exposed to air for several months, 1·3 g. of *trans*-diol and 14 g. of "*cis*-fraction," d^{23} 1·003, n_D^{23} 1·484, α_D −38·6°, were obtained.

Fractionation of E. dives *Residues.*—(*a*) Diols from last runnings of the piperitone distillation (71 lb.; α_D 0; $d_D^{15\cdot5}$ 0·970) were stirred with three lots each of 3·5 gallons of hot water. The combined aqueous layers, after being washed with a petroleum solvent, were concentrated as previously described, yielding fractions (i) (19·5 g.) b. p. 130°/4 mm., α_D −46·9°, $n_D^{18\cdot5}$ 1·485, (ii) (28·5 g.) b. p. 133°/4 mm., α_D −49·2°, $n_D^{18\cdot5}$ 1·4952, (iii) (8 g.), b. p. 135°/5 mm., α_D −51·3°, $n_D^{18\cdot5}$ 1·486, (iv) (18 g.) b. p. 140°/5 mm., α_D −51·5°, $n_D^{18\cdot5}$ 1·496, (v) (9 g.) b. p. 148°/5 mm., and a residue (6 g.).

(*c*) 1200 Lb. of residues from the distillation of *E. dives* oil were extracted as previously described. The corresponding "*cis*-fraction" had α_D −31·6°. 37 G. of *trans*-diol were also obtained.

Another extraction of 90 lb. of a similar fraction from the piperitone distillation gave a "*cis*-fraction," α_D −47·0°.

(trans)-p-*Menth*-1-*ene*-3 : 6-*diol.*—The specimens from phellandrene and *E. dives* oil had the same m. p. and α_D, in accord with those of Dupont (*loc. cit.*).

Acetylation. Heating the diol (5 g.) and 15 g. of acetic anhydride (15 g.) under gentle reflux for 2 hours gave 7 g. of *diacetate*, needles, m. p. 28°, b. p. 148—149°/4 mm., α_D +69·15°, $n_D^{27\cdot5}$ 1·4610 (Found: ester value, 438·5 ≡ 99·65%), whence hydrolysis with alcoholic sodium hydroxide regenerated the original diol.

Hydrogenation. A concentrated alcoholic solution of *trans-p*-menth-1-ene-3 : 6-diol was hydrogenated in a shaking vessel at atmospheric pressure, in presence of a neutral nickel catalyst, until no further absorption occurred (15 g. of diol absorbed 1800 c.c. of hydrogen). trans-p-*Menthane*-3 : 6-*diol* crystallised in shiny needles, m. p. 137°, α_D^{21} +32·8° (*c*, 0·0783 in ethanol), from ethanol in which it was more soluble than the original glycol; it was also more soluble in water, but very sparingly soluble in benzene or light petroleum (Found: C, 69·4; H, 11·7. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

Oxide.—Steam was passed through a mixture of the *trans*-diol (20 g.) and 0·5% sulphuric acid (100 c.c.) while the volume was kept constant. 17 G. of the distillate were stirred with a saturated aqueous solution of sodium sulphite (28 g. of anhydrous) and sodium hydrogen carbonate (19 g.) for 6 hours. After filtration and separation, the product (14 g.) was recovered and distilled at 6 mm., giving fractions (*a*) (3·5 g.), α_D −33·4°, (*b*) (2·5 g.), α_D −58·6°, (*c*) (7·0 g.) α_D −88·6°, and a residue (1 g.). Fraction (*c*) when redistilled gave the pure *oxide* (IV), $[\alpha]_D$ −95·68°, n_D^{20} 1·4775, and $d_{15\cdot5}^{22}$ 0·926 (Found: C, 78·4; H, 10·6; $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%).

When the oxide was kept in a sealed tube for several months, $[\alpha]_D$ changed to −90°. Water was evolved when the oxide was distilled at atmospheric pressure; bromination did not give a satisfactory product.

Fractions (*a*) and (*b*) were heated on a water-bath for 20 minutes with an equal weight of 90% formic acid and then washed until neutral. The residue (5 g.) was shaken with aqueous sodium sulphite–sodium hydrogen carbonate as described above. The solution was filtered, and extracted with light petroleum. The petroleum layer yielded an oil (2·5 g.), which, when distilled over sodium, had the odour, b. p., and n_D of *p*-cymene. When the aqueous solution was boiled for a short time with sodium carbonate and extracted with ether, it yielded carvotanacetone (1·3 g.), α_D −43·8° (semicarbazone, m. p. 174°).

cis-p-*Menth*-1-*ene*-3 : 6-*diol.*—The "*cis*-fractions" could not be induced to crystallise. When, however, those with the highest lævorotation (−51·5°) were kept in contact with water for many days at temperatures slightly above 0°, well-shaped crystals of a hydrate formed; when spread on a porous tile, these rapidly became sticky. This hydrate could then be easily isolated from the autoxidation products of phellandrene, as well from "*cis*-fractions" of varying rotation, those having the greatest lævorotation giving the highest yield. Recrystallised from water, it melted at 27° and did not become sticky when kept at +8°. It is more soluble in cold than in hot water. The aqueous solution froths when shaken. Attempts to determine the water of crystallisation by keeping the hydrate in an evacuated desiccator over phosphoric oxide gave values corresponding to approximately 3 molecules, but were erratic because this substance loses water in air, even at 8°. The hydrate was readily dehydrated by heating at 100 mm.; the anhydrous cis-*diol* thus obtained distilled mainly at 136—137°/4 mm. and then had $[\alpha]_D$ (liquid) −51·5° and crystallised readily. Recrystallised from benzene, it had m. p. 53·5—54°,

$[\alpha]_D^{23\cdot5}$ −33·6° (*c*, 0·1031 in ethanol) (Found: C, 70·05; H, 10·9. $C_{10}H_{18}O_2$ requires C, 70·55; H, 10·7%). When the *cis*-diol was distilled at atmospheric pressure, partial decomposition occurred; the first distillate, which had an odour of cymene and of the oxide from the *trans*-diol, did not react with semicarbazide but, after treatment with formic acid, gave a semicarbazone which did not depress the m. p. of that of carvotanacetone.

Acetylation. The anhydrous glycol (6 g.) and acetic anhydride (8 g.) were heated under gentle reflux for 2 hours and then fractionated, yielding fractions (i) b. p. up to 100°/110 mm. (12 g.), (ii) b. p. 115°/6·5 mm. (3 g.), and (iii) b. p. 140°/6·5 mm. (5·5 g.). Fractions (ii) and (iii) were combined, washed until neutral, and dried. The resultant diacetate had α_D −128·8°, the ester value (337·7) corresponding to 85·6% purity.

Hydrogenation. This was carried out as for the *trans*-diol. The distilled saturated product did not at once crystallise but, when shaken with water, gave a crystalline *trihydrate* (Found: loss over sulphuric acid in a vacuum, 23·7%. $C_{10}H_{20}O_2,3H_2O$ requires H_2O, 23·9%), which, when recrystallised from water, formed shiny plates, m. p. 58—59°. At room temperature these soon changed into an amorphous powder which was recrystallised from benzene, giving anhydrous cis-p-*menthane*-3 : 6-*diol* as prisms, m. p. 88—89°, $[\alpha]_D^{21}$ +32·7° in ethanol (Found: C, 69·4; H, 11·95. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

Oxidation. The anhydrous *cis*-diol (2·55 g.) was shaken with water (15 c.c.). While this mixture was cooled, a mixture of potassium dichromate (9 g.), sulphuric acid (12 g.), and water (40 c.c.) was slowly added. Reaction ended in 1½ hours. The green solution was twice extracted with benzene and the extract steam-distilled. Treatment of the yellow distillate with semicarbazide gave thymoquinone monosemicarbazone, m. p. 202° (decomp.), whereas the residue from the distillation gave the semicarbazone, m. p. 185—186°, of the C_9 lactone of Henry and Paget (*loc. cit.*). M. p.s were undepressed on admixture with the semicarbazones of the corresponding oxidation products of the *trans*-diol.

Addendum by Rex T. Prider.

Crystallography and Optical Constants of trans-p-*Menth*-1-*ene*-3 : 6-*diol*.—The optical and goniometrical examination of crystals of the *trans*-diol indicate that this compound belongs to

Fig. 1.

Optic orientation of trans-p-*menth*-1-*ene*-3 : 6-*diol*.

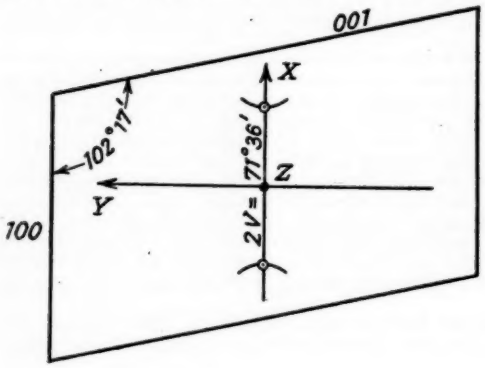
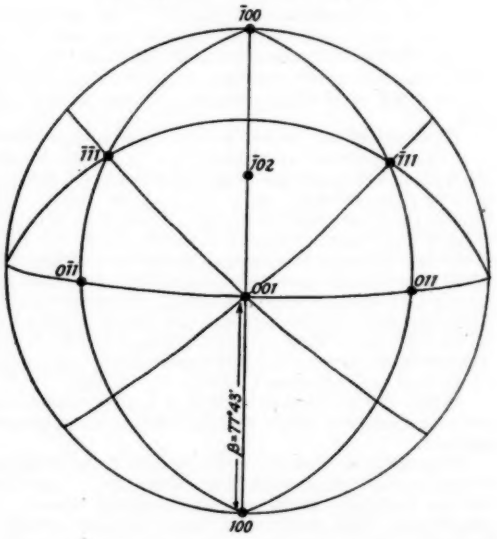


Fig. 2.

Stereogram of forms developed: trans-p-*menth*-1-*ene*-3 : 6-*diol*.



the normal class of the monoclinic system. The optical properties (all constants determined for sodium light) are: colourless, biaxial, positive optical character; n (by immersion in oils), $\gamma = 1{\cdot}591 \pm 0{\cdot}001$, $\beta = 1{\cdot}540 \pm 0{\cdot}001$, $\alpha = 1{\cdot}516 \pm 0{\cdot}001$, $\gamma - \alpha = 0{\cdot}075$; optic axial angle (by Fuess axial-angle apparatus) $(+)2V = 71°\ 36'$; dispersion of the optic axes is noticeable $r > v$, but there is no noticeable dispersion of the bisectrices; optic elongation of acicular crystals and cleavage fragments is positive.

The optic orientation (Fig. 1) is: $Z = b$, $X = c$ (approximately), opt. ax. pl. ⊥ 010.

The following three distinct crystallographic habits were noted in the material examined.

(i) Single crystals, up to 4 × 4 × 2½ mm., completely bounded by rather dull-lustred faces, tabular parallel to the base (001). These crystals show the development of the base (001), clinodome (011), orthopinacoid (100), and hemipyramid ($\bar{1}11$), and have cleavage parallel to

(001), (100), and (011). The dull-lustred faces did not permit of accurate determination of the interfacial angles on the two-circle goniometer, but the following table gives the average angles when the crystal was set with the base (001) normal to the vertical circle axis:

Face.*	ρ.	ϕ.	Face.*	ρ.	ϕ.
001	0° 00′	—	$\bar{1}11$	80° 35′	48° 30′
$\bar{1}00$	102° 00′	0° 00′	$0\bar{1}1$	67° 48′	270° 00′
100	78° 00′	180° 00′	011	67° 48′	90° 00′
$\bar{1}\bar{1}1$	80° 35′	311° 30′			

* Indices on assumption that the hemipyramid is the unit form ($\bar{1}11$).

Thus $\beta = 78° 00'$, and the axial ratio $b : c = 1{\cdot}000 : 2{\cdot}503$.

(ii) Cleavage plates, measuring on the average $5 \times 5 \times \frac{1}{2}$ mm., with highly perfect basal (001) cleavage giving the substance a micaceous habit. In addition this form has very good (100) cleavage and fair (010) or (011) cleavage. As a result, when crushed for optical examination in oils, it cleaves into extremely thin prisms elongated parallel to *b*, which have straight extinction and positive optical elongation. On this material the refractive indices γ and β' were measured by immersion in oils but, because of the highly perfect basal cleavage, α cannot be conveniently determined. The optic axial angle quoted above was determined on this material. Measurement of the angles between the cleavages on the single-circle goniometer gave $(001) \wedge (100) = 77° 51'$.

(iii) Acicular crystals, up to 10 mm. long and 0·15 mm. in diameter, with brilliantly reflecting faces parallel to the axis of the needle and terminated by two extremely small faces. These needles are elongated parallel to the ortho-axis (*b*) and all have straight extinction and positive optical elongation. When immersed in oils, some lie on the orthopinacoid (100) and some on the base (001). As a result the refractive index α is best determined in this crop of crystals (*i.e.*, in those crystals lying on 100). The interfacial angles of these acicular crystals were measured on the two-circle goniometer with the following results (the crystal was mounted with the long axis (*b*) parallel to the vertical circle axis):

Face.	ρ.	ϕ.	Face.	ρ.	ϕ.
001	0° 00′	0° 00′	$\bar{1}00$	0° 00′	102° 17′
100	0° 00′	282° 17′	$\bar{1}02$	0° 00′	54° 50′
$10\bar{2}$	0° 00′	234° 50′	011	67° 42′	0° 00′
$00\bar{1}$	0° 00′	180° 00′	$01\bar{1}$	67° 42′	180° 00′

Thus the significant interfacial angles are: $001 \wedge 100 = 77° 43'$; $001 \wedge \bar{1}02 = 54° 50'$; $001 \wedge 011 = 67° 42$. Thence the following axial elements were calculated: $a : b : c = 1{\cdot}124 : 1{\cdot}000 : 2{\cdot}496$; $\beta = 77° 43'$. These values are in fair agreement with the figures obtained from the larger crystal with duller faces. In view of the more brilliant facets on the acicular crystals the crystallographic data from them are the more accurate.

The crystallographic data for this compound may be summarised thus. Monoclinic, normal class. Axial elements, $a : b : c = 1{\cdot}124 : 1{\cdot}000 : 2{\cdot}496$; $\beta = 77°43'$. Interfacial angles: $001 \wedge 100 = 77° 43'$; $001 \wedge \bar{1}02 = 54° 50'$; $001 \wedge 011 = 67° 42'$; $001 \wedge \bar{1}11 = 80° 35'$; $\bar{1}11 \wedge \bar{1}\bar{1}1 = 97° 00'$. Cleavage: 001 highly perfect; 100 very good; 010 (or 011) fair. Habit either tabular ‖001 (showing development of 001, 100, 011, $\bar{1}11$) or acicular elongated parallel to the ortho-axis (showing development of 001, 100, $\bar{1}02$ and minor development of 011).

A stereogram of the forms developed on this compound is shown in Fig. 2.

We thank Messrs. Plaimar Ltd. for having provided the facilities to carry out the experimental work, Professor R. Prider, University of Western Australia, for the determination of the crystallographic properties of the *trans*-glycol, Mr. F. H. Morrison, Economic Chemist at the Sydney Museum of Technology and Applied Science for his valuable assistance in obtaining the micro-analyses, and Dr. Y.-R. Naves, Geneva, for his kind help.

2, Parkway, Nedlands, W. Australia. [*Received, February 14th*, 1949.]

437. *Isomerisation Reactions. Part II.*

By G. M. Badger, W. Carruthers, and J. W. Cook.

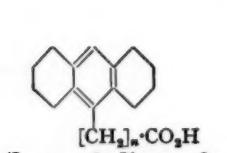
The structural requirements for the isomerisation of derivatives of *s*-octahydroanthracene by treatment with anhydrous hydrogen fluoride have been investigated. Compounds of type (I), in which $n = 2$ or 3, but not when $n = 1$, underwent simultaneous isomerisation and cyclisation in good yield. Compounds of type (III; R = H, alkyl, or CO_2H) were not isomerised; nor were compounds of type (IV; R = H or Me).

In the presence of aluminium chloride, in carbon disulphide solution, succinic anhydride and *s*-octahydroanthracene interacted to give β-(9-*s*-octahydrophenanthroyl)propionic acid. In tetrachloroethane, a mixture of the same acid and β-(9-s-*octahydroanthroyl*)*propionic acid* was obtained.

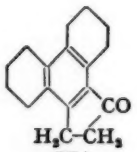
Cyclisation of β-(1 : 2 : 3 : 4-tetrahydro-9-phenanthryl)propionic acid (X) with hydrogen fluoride, with stannic chloride, or with aluminium chloride, gave the ketone (XII) and not the isomeric ketone (XI).

The discovery of a new type of reaction with anhydrous hydrogen fluoride, namely the isomerisation and cyclisation of *s*-octahydroanthranylpropionic acid (I*b*) to 1′-keto-9 : 10-*cyclo*penteno-*s*-octahydrophenanthrene (II) was reported by Badger, Carruthers, Cook, and Schoental (this vol., p. 169). Neither *s*-octahydroanthracene nor its 9-carboxylic acid underwent isomerisation under the same conditions, results which indicated that cyclisation may be an important part in the mechanism of the rearrangement. In this respect, therefore, the isomerisation appeared to differ from the somewhat analogous rearrangements long known to take place with aluminium chloride and sulphuric acid. Treatment of octahydroanthracene with aluminium chloride, for example, yields an equilibrium mixture of octahydroanthracene and octahydrophenanthrene (Schroeter, *Ber.*, 1924, **57**, 1990), and Schroeter and Götzky (*Ber.*, 1927, **60**, 2035) have effected the conversion of *s*-octahydroanthracene-9-sulphonic acid into *s*-octahydrophenanthrene-9-sulphonic acid by means of sulphuric acid. Nevertheless, the three types of reaction have many features in common, especially as it has now been found that isomerisation and cyclisation of the chloride of *s*-octahydroanthranylpropionic acid (I*b*) into the ketone (II) may also be achieved by the action of aluminium chloride under mild conditions.

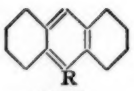
Probably the closest analogy to the hydrogen fluoride transformations which we have studied is furnished by the displacement of alkyl groups by acyl groups by means of aluminium chloride (v. Auwers and Mauss, *Annalen*, 1928, **460**, 240; Hennion and McLeese, *J. Amer. Chem. Soc.*, 1942, **64**, 2421).



(I*a*, $n = 1$; I*b*, $n = 2$; I*c*, $n = 3$.)



(II.)



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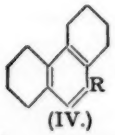

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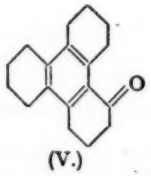

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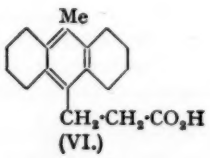


(VI.)

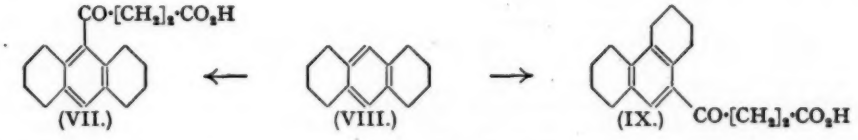
We have also extended our investigation on the effect of anhydrous hydrogen fluoride to several compounds related to octahydroanthranylpropionic acid, to provide some of the data necessary for an interpretation of the mechanism of the reaction. No isomerisation could be detected after treatment of 9-*methyl*- or 9-*ethyl*-s-*octahydroanthracene* or 9-s-*octahydroanthranylacetic acid* (I*a*) with hydrogen fluoride at room temperature; as previously recorded, neither the parent hydrocarbon nor its 9-carboxylic acid derivative was found to rearrange. Furthermore, *s*-octahydrophenanthrene and its 9-*methyl* derivative were unaffected, a result which excludes the possibility that there is an equilibrium, but displaced very much in the direction of the octahydroanthracene derivatives.

Isomerisation with simultaneous cyclisation has, however, been achieved with γ-(9-s-*octahydroanthranyl*)*butyric acid* (I*c*), 1-keto-*s*-dodecahydrotriphenylene (V) being isolated in excellent

yield. Moreover, Aitken, Badger, and Cook (future communication) have found that duryl-propionic acid also undergoes a similar reaction, although durene itself remains unaffected by hydrogen fluoride at room temperature. It therefore appears to be established that, at room temperature, the cyclisation is an essential factor in the rearrangement. This is in harmony with the findings of Calcott, Tinker, and Weinmayr (*J. Amer. Chem. Soc.*, 1939, **61**, 1010) that migration of alkyl groups attached to benzene rings does not occur in the presence of hydrogen fluoride at ordinary temperatures. It is noteworthy, however, that toluene may be prepared on a large scale by treatment of a mixture of xylene and benzene with hydrogen fluoride at high temperatures and pressures (U.S.P. 2,416,184).

It appeared to be of interest to attempt the isomerisation and cyclisation of β-(10-*methyl*-s-*octahydro*-9-*anthranyl*)*propionic acid* (VI), as such a rearrangement would necessarily involve the displacement of the methyl group. Treatment of this acid with hydrogen fluoride did indeed give rise to a neutral ketonic mixture, from which it was not found possible to isolate any pure constituent.

For the preparation of γ-(9-*s*-octahydroanthranyl)butyric acid (I*c*), we have used two methods. (I$_c$) was prepared, without difficulty, *via* γ-(9-s-*octahydroanthranyl*)*butyramide*, from the corresponding propionic acid (I*b*) by the Arndt–Eistert procedure. It has also been obtained by Clemmensen reduction of β-(9-s-*octahydroanthroyl*)*propionic acid*. In the preparation of this intermediate, we have observed another type of isomerisation. The product of the interaction of octahydroanthracene and succinic anhydride, in carbon disulphide, with aluminium chloride was not the expected octahydroanthroylpropionic acid (VII), but the corresponding derivative of octahydrophenanthrene (IX). Moreover, when the reaction was carried out in tetrachloroethane, at the same temperature, both products were isolated from the resulting mixture. This isomerisation is of interest as Arnold and Barnes (*J. Amer. Chem. Soc.*, 1944, **66**, 960) found that acetic anhydride reacts with octahydroanthracene in tetrachloroethane, with aluminium chloride, without isomerisation, to give 9-acetyl-*s*-octahydroanthracene. We have confirmed this result, and have also examined the reaction in carbon disulphide, under the same conditions, and with the same proportions of reactants, as led to isomerisation and condensation in the succinic anhydride experiment. In this case, however, no reaction occurred, and further investigation is desirable.



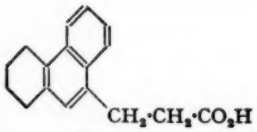
9-Ethyl-*s*-octahydroanthracene (III; R = Et) was prepared from the 9-acetyl compound by Clemmensen reduction, and its structure was confirmed by its dehydrogenation to 9-ethyl-anthracene. 9-Chloromethyl-*s*-octahydroanthracene was used to prepare the 9-methyl-*s*-octahydroanthracene (Badger *et al.*, *loc. cit.*) and also for the preparation of 9-*cyanomethyl*-s-*octahydroanthracene*, from which 9-*s*-octahydroanthranylacetic acid (I*a*) was obtained by hydrolysis. Chloromethylation of 9-methyl-*s*-octahydroanthracene gave 9-*methyl*-10-*chloromethyl*-s-*octahydroanthracene*, which was condensed with ethyl malonate, the product being hydrolysed and decarboxylated to give β-(10-methyl-*s*-octahydro-9-anthranyl)propionic acid (VI).

Chloromethylation of *s*-octahydrophenanthrene gave 9-*chloromethyl*-s-*octahydrophenanthrene*, together with a little 9 : 10-*bischloromethyl*-s-*octahydrophenanthrene*. Reduction with hydrogen and palladium gave 9-methyl- and 9 : 10-*dimethyl*-s-*octahydrophenanthrene*, respectively.

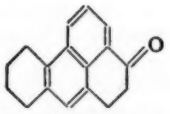
Experiments on the cyclisation of β-(1 : 2 : 3 : 4-tetrahydro-9-phenanthryl)propionic acid (X) (Bachmann and Cronyn, *J. Org. Chem.*, 1943, **8**, 456) have also been carried out. This acid, for which the structure was established by the American workers, might conceivably cyclise to give either (XI) or (XII). The acid can be regarded as a naphthalene derivative, analogous to a β-1-naphthylpropionic acid having two alkyl substituents. The cyclisation of naphthylpropionic acid can theoretically take place in either the 2- or the 8-position, but, in fact, it is known to take place almost exclusively in the 8-position, although a small proportion of the isomeric product is also formed (Fieser and Gates, *J. Amer. Chem. Soc.*, 1940, **62**, 2335). Again, Buu-Hoï and Cagniant (*Rev. Sci.*, 1941, **79**, 644) showed that treatment of β-(4-methyl-1-naphthyl)propionyl chloride with aluminium chloride gave 6-methylperinaphthan-1-one,* none

* Buu-Hoï and Cagniant numbered this compound 3-methylperinaphthan-7-one. For numbering used here see this vol., p. 1768.

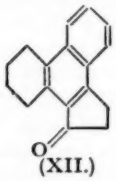
of the alternative product being isolated. The formation of this product involves cyclisation into the 8-position of the naphthalene system.



(X.)



(XI.)



(XII.)

These, and other known examples, illustrate the readiness with which cyclisation of β-1-naphthylpropionic acids takes place in the 8-position. This orientation is favoured both by the well-known preference for the formation of six-membered rather than five-membered rings in intramolecular acylations, and by the tendency for cyclisation to take place in the most reactive centre available. It was therefore expected that tetrahydrophenanthrenepropionic acid (X) would cyclise to give the ketone (XI) rather than the alternative ketone (XII). In fact, however it has been found that the opposite is the case, for cyclisation with hydrogen fluoride, with stannic chloride, or with aluminium chloride all resulted in the formation of the ketone (XII) in satisfactory yield. The structure of this compound was proved by its reduction to 9 : 10-cyclo*penteno*-1 : 2 : 3 : 4-*tetrahydrophenanthrene*, which on dehydrogenation gave the known 9 : 10-*cyclo*pentenophenanthrene.

It may be that the tetramethylene ring activates the 10-position to such an extent that cyclisation into this position, with formation of a five-membered ring, is preferred.

Experimental.

Isomerisation and Cyclisation of Octahydroanthranylpropionic Acid (Ib) *by the Friedel–Crafts Method.*—β-(9-*s*-Octahydroanthranyl)propionic acid (1 g.) was converted into the chloride, which was then treated with aluminium chloride, in nitrobenzene, exactly as described for octahydrophenanthrylpropionic acid by Badger, Carruthers, Cook, and Schoental (*loc. cit.*). The product was worked up in the usual way. Crystallisation from ethanol gave 1′-keto-9 : 10-*cyclo*penteno-*s*-octahydrophenanthrene as colourless needles, m. p. 193—195°, not depressed by an authentic specimen prepared from β-(9-*s*-octahydrophenanthryl)propionic acid by the Friedel–Crafts method.

Condensation of s-Octahydroanthracene with Succinic Anhydride.—(a) *In carbon disulphide.* Powdered aluminium chloride (18·4 g.) was added gradually, during ½ hour, to an ice-cold suspension of *s*-octahydroanthracene (VIII) (12·4 g.) and succinic anhydride (8 g.) in carbon disulphide (132 c.c.). After 4 hours in an ice-bath the mixture was left overnight at room temperature, and then warmed to 45° for 15 minutes. Carbon disulphide was decanted from the cooled mixture and the residual gummy complex decomposed with ice and hydrochloric acid. After extraction with dilute sodium carbonate the crude acidic product (14 g.) was reprecipitated, and recrystallised from acetic acid and then ethanol. β-(9-*s*-Octahydrophenanthroyl)propionic acid (IX) (9·8 g.) was obtained as colourless glistening needles, m. p. 143—144°, alone or mixed with an authentic specimen prepared from *s*-octahydrophenanthrene and succinic anhydride (Van de Kamp, Burger, and Mosettig, *J. Amer. Chem. Soc.*, 1938, **60**, 1321). The same acid was obtained when the reaction was carried out with omission of the short period of heating. Reduction of this keto-acid (8·5 g.) by heating it under reflux for 24 hours with amalgamated zinc (30 g.), concentrated hydrochloric acid (100 c.c.), acetic acid (20 c.c.), and toluene (30 c.c.) gave γ-(9-*s*-octahydrophenanthryl)butyric acid, b. p. 240°/2 mm. (6 g.), m. p. 128—129°, from ethanol (lit., m. p. 128—129°). Cyclisation of this acid (1·5 g.) with anhydrous hydrogen fluoride gave 1-keto-*s*-dodecahydrotriphenylene (1·42 g.), which crystallised from alcohol in long colourless needles, m. p. 222° (lit., m. p. 222—222·5°).

(b) *In tetrachloroethane.* *s*-Octahydroanthracene (VIII) (3·1 g.) was added to a well-stirred suspension of powdered aluminium chloride (10 g.) in dry tetrachloroethane (30 c.c.). After cooling in a freezing mixture, a slurry of succinic anhydride (3·7 g.) in tetrachloroethane (50 c.c.) was added. The mixture was stirred, with cooling, for several hours, and then left overnight. After decomposition with ice and hydrochloric acid, and removal of the solvent in steam, the crude product was extracted with boiling dilute sodium carbonate, and the acid reprecipitated. Recrystallisation from acetic acid gave β-(9-*s*-*octahydroanthroyl*)*propionic acid* (VII) (2·5 g.) which, after further recrystallisation from acetic acid and from ethanol, formed colourless prismatic needles, m. p. 210° (Found: C, 75·6; H, 7·8. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%). Addition of water to the mother-liquors of the initial crystallisation gave, after standing overnight, β-(9-*s*-octahydrophenanthroyl)propionic acid (1·4 g.), m. p. 143—144° alone or mixed with an authentic specimen prepared as described in (a).

γ-(9-*s*-*Octahydroanthranyl*)*butyric Acid* (Ic).—(a) *Arndt–Eistert method.* A mixture of octahydroanthranylpropionic acid (2·2 g.; Badger, Carruthers, Cook, and Schoental, *loc. cit.*), thionyl chloride (2·5 c.c.), and a few drops of pyridine in dry benzene (6 c.c.) was warmed at 50—60° for 2 hours. The crystalline solid obtained on removal of the excess of thionyl chloride and benzene *in vacuo* was dissolved in dry benzene (10 c.c.) and slowly added to a stirred, ice-cold solution of diazomethane (from 7 g. of nitrosomethylurea) in ether (150 c.c.). After some hours, the ether and excess of diazomethane were allowed to evaporate at room temperature. The yellow crystalline diazo-ketone so obtained, dissolved in dioxan (15 c.c.), was added to a 20% solution of ammonia (15 c.c.) and 10% aqueous silver nitrate (3 c.c.), and the mixture heated on the steam-bath for 2½ hours. The dark mixture was diluted with

dioxan (15 c.c.) and boiled with charcoal. After filtration and dilution with water, *γ-(9-s-octahydroanthranyl)butyramide* (1·7 g.) separated. It crystallised from benzene–light petroleum in soft white needles, m. p. 163—164° (Found: C, 79·9; H, 9·2; N, 5·3. $C_{18}H_{25}ON$ requires C, 79·7; H, 9·2; N, 5·2%). Hydrolysis of the amide (1·15 g.) by heating it under reflux for 12 hours with potassium hydroxide (5 g.) in ethanol (50 c.c.) gave *γ-(9-s-octahydroanthranyl)butyric acid* (1 g.), which crystallised from ethanol as fine colourless needles, m. p. 152° (Found: C, 79·5; H, 8·9. $C_{18}H_{24}O_2$ requires C, 79·4; H, 8·8%).

(b) *By reduction of octahydroanthroylpropionic acid.* A mixture of the acid (2·5 g.), amalgamated zinc (10 g.), concentrated hydrochloric acid (75 c.c.), acetic acid (10 c.c.), and toluene (15 c.c.) was heated under reflux for 24 hours. The product was isolated in the usual way, and after distillation at 185°/1 mm., it crystallised from acetic acid in colourless needles, m. p. 148—150°, alone or mixed with authentic octahydroanthranylbutyric acid prepared as described above.

Isomerisation and Cyclisation of Octahydroanthranylbutyric Acid.—This acid (0·5 g.) was treated with anhydrous hydrogen fluoride (*ca.* 20 c.c.) at room temperature for 12 hours. The product was dissolved in benzene and washed with caustic alkali. No acidic material was recovered from the alkaline extract. The neutral material obtained on removal of the benzene was recrystallised from ethanol. 1-Keto-*s*-dodecahydrotriphenylene (0·39 g.) was obtained as colourless needles, m. p. and mixed m. p. with an authentic specimen, 222° (lit., m. p. 222—222·5°).

9-Acetyl-s-octahydroanthracene (III; R = Ac).—The method of Arnold and Barnes (*J. Amer. Chem. Soc.*, 1944, **66**, 960), involving the interaction of acetic anhydride and *s*-octahydroanthracene with aluminium chloride in tetrachloroethane solution, was found to be satisfactory.

9-Ethyl-s-octahydroanthracene (III; R = Et).—9-Acetyl-*s*-octahydroanthracene (1·5 g.), amalgamated zinc (10 g.), toluene (10 c.c.), acetic acid (10 c.c.), and concentrated hydrochloric acid (50 c.c.) were heated under reflux for 24 hours. The cooled mixture was extracted with benzene, the benzene evaporated, and the product distilled. *9-Ethyl-s-octahydroanthracene*, redistilled for analysis, b. p. 140° (air-bath temp.)/2 mm., was obtained as a colourless liquid (Found: C, 90·1; H, 9·9. $C_{16}H_{22}$ requires C, 89·7; H, 10·3%).

After dehydrogenation of a specimen (0·16 g.) with palladium-black at 300° for 30 minutes in an atmosphere of carbon dioxide, the product was dissolved in ethanol, and a small amount of a white solid, m. p. 210°, filtered off. This was identified as anthracene by comparison with an authentic specimen. The ethanolic filtrate was treated with picric acid, and the picrate recrystallised from ethanol. It formed red-yellow needles, m. p. 120° (lit., m. p. of 9-ethylanthracene picrate, 120°). Decomposition of the picrate on alumina gave 9-ethylanthracene as colourless needles, m. p. 63—64° (lit., m. p. 64°), from ethanol.

Treatment of 9-ethyl-*s*-octahydroanthracene with anhydrous hydrogen fluoride at room temperature for 15 hours gave an oil, which was dehydrogenated as above. Only 9-ethylanthracene could be detected in the product.

9-Methyl-s-octahydroanthracene (III; R = Me).—Methyloctahydroanthracene was prepared by reduction of the chloromethyl derivative as described by Badger, Carruthers, Cook, and Schoental (*loc. cit.*). As a further check on the homogeneity of the product obtained in the chloromethylation experiments, the following transformation were carried out. *9-Acetoxymethyl-s-octahydroanthracene* (2·4 g.) was obtained when 9-chloromethyloctahydroanthracene (2·2 g.) and anhydrous potassium acetate (2·2 g.) were heated in boiling glacial acetic acid (100 c.c.) for 2 hours. It formed colourless, flat, glistening needles, m. p. 73°, from ethanol (Found: C, 78·9; H, 8·6. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·5%). Hydrolysis of the acetoxy-compound (1·5 g.) with alcoholic potassium hydroxide gave *9-hydroxymethyl-s-octahydroanthracene* (1·2 g.) as colourless prismatic needles, m. p. 114°, from ethanol (Found: C, 83·5; H, 9·2. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%). Passage of hydrogen chloride through a solution of this compound in benzene (containing an equal weight of anhydrous calcium chloride) gave the 9-chloromethyl compound, identical with that obtained by direct chloromethylation of *s*-octahydroanthracene.

9-Cyanomethyl-s-octahydroanthracene.—A mixture of 9-chloromethyl-*s*-octahydroanthracene (1·2 g.) and potassium cyanide (3 g.) in ethanol (15 c.c.) and water (5 c.c.) was refluxed for 2½ hours. *9-Cyanomethyl-s-octahydroanthracene* (1 g.) formed colourless lustrous plates, m. p. 108—109°, from ethanol (Found: C, 85·6; H, 8·3; N, 6·3. $C_{16}H_{19}N$ requires C, 85·3; H, 8·4; N, 6·2%).

9-s-Octahydroanthranylacetic acid (Ia).—The above nitrile (0·9 g.) was heated at 150—160° for 10 hours in a mixture (50 c.c.) of equal volumes of water, acetic acid, and concentrated sulphuric acid. The *acid* (0·8 g.) formed colourless plates, m. p. 212—214° (decomp.) after sintering at 190° (Found: C, 78·6; H, 8·4. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%). It was recovered unchanged after treatment with anhydrous hydrogen fluoride at room temperature.

9-Methyl-10-chloromethyl-s-octahydroanthracene.—Hydrogen chloride was passed into a suspension of paraformaldehyde (1·2 g.) in glacial acetic acid (20 c.c.) until a clear solution was obtained. 9-Methyl-*s*-octahydroanthracene (6 g.) was added, and the passage of hydrogen chloride continued, the temperature being maintained at 60—70°. After 2 hours, the crystals (6·7 g.) were collected, washed with water, and recrystallised from benzene–light petroleum. *9-Methyl-10-chloromethyl-s-octahydroanthracene* formed colourless plates, m. p. 143—144° (Found: C, 77·1; H, 8·1. $C_{16}H_{21}Cl$ requires C, 77·3; H, 8·45%).

Attempted recrystallisation of this compound from ethanol led to the formation of *9-methyl-10-ethoxymethyl-s-octahydroanthracene*, which formed fluffy colourless needles, m. p. 73° (Found: C, 83·7; H, 9·8. $C_{18}H_{26}O$ requires C, 83·7; H, 10·1%).

The chloromethyl compound, in acetone, was smoothly reduced with hydrogen and palladium-black to 9 : 10-dimethyl-*s*-octahydroanthracene, identical with a specimen prepared by Badger, Carruthers, Cook, and Schoental (*loc. cit.*).

β-(10-Methyl-s-octahydro-9-anthranyl)propionic Acid (VI).—A mixture of atomised sodium (1·1 g.), ethyl malonate (7·5 g.), and dry benzene (25 c.c.) was heated under reflux for 2 hours. 9-Methyl-10-chloromethyl-*s*-octahydroanthracene (5 g.) in dry benzene (35 c.c.) was added, and the refluxing continued for a further 8 hours. After removal of the benzene, the ester was hydrolysed by 3 hours' boiling with

potassium hydroxide (15 g.) in aqueous ethanol (1 : 1; 100 c.c.). After decarboxylation of the acidic product by heating at 240° for 15 minutes, *β*-(10-*methyl*-s-*octahydro*-9-*anthranyl*)*propionic acid* (3·2 g.) was obtained. It crystallised from acetic acid in long colourless needles, m. p. 206—208° after sintering (Found: C, 79·4; H, 8·7. $C_{18}H_{24}O_2$ requires C, 79·4; H, 8·8%).

Treatment of this acid with anhydrous hydrogen fluoride resulted in its conversion into a neutral ketonic, but gummy, product. Attempted distillation led to extensive decomposition, and chromatography gave no purification. It formed a solid oxime and dinitrophenylhydrazone, but neither product could be isolated in a pure condition.

9-*Chloromethyl*-s-*octahydrophenanthrene* (IV; R = CH_2Cl).—Hydrogen chloride was passed into a vigorously stirred mixture of *s*-octahydrophenanthrene (8 g.; Durland and Adkins, *J. Amer. Chem. Soc.*, 1937, **59**, 135), aqueous formaldehyde (8 c.c., 40%), concentrated hydrochloric acid (40 c.c.), and acetic acid (5 c.c.) at 70° for 5½ hours. The cooled mixture was extracted with benzene, and the extract was washed, dried, and distilled. After removal of some unchanged hydrocarbon, a colourless oil (5 g.) was collected at 170—180°/1·5 mm. Crystallisation from light petroleum gave 9-*chloromethyl*-s-*octahydrophenanthrene* as clusters of colourless prismatic needles, m. p. 56° (Found: C, 76·8; H, 8·2. $C_{15}H_{19}Cl$ requires C, 76·8; H, 8·1%). The residue from the distillation was extracted with light petroleum and gave 9 : 10-*bischloromethyl*-s-*octahydrophenanthrene* (0·8 g.) as colourless needles, m. p. 160° from ethanol, in which solvent it is sparingly soluble (Found: C, 67·9; H, 6·9. $C_{16}H_{20}Cl_2$ requires C, 68·1; H, 7·1%).

9-*Methyl*-s-*octahydrophenanthrene* (IV; R = Me).—Reduction of chloromethyloctahydrophenanthrene, in acetone, with hydrogen and palladium proceeded smoothly to give 9-*methyl*-s-*octahydrophenanthrene* as a colourless oil, b. p. 106—110° (air-bath temp.)/0·3 mm. (Found: C, 90·0; H, 9·9. $C_{15}H_{20}$ requires C, 90·0; H, 10·0%). Dehydrogenation with palladium-black at 280° for 3 hours gave 9-methylphenanthrene, identified by comparison with an authentic specimen. In the same way, reduction of the bischloromethyl derivative gave 9 : 10-*dimethyl*-s-*octahydrophenanthrene* as colourless glistening plates, m. p. 98°, from ethanol (Found: C, 89·75; H, 10·3. $C_{16}H_{22}$ requires C, 89·7; H, 10·3%).

After treatment with anhydrous hydrogen fluoride, 9-methyl-*s*-octahydrophenanthrene was recovered unchanged, for dehydrogenation of the resulting oil gave only 9-methylphenanthrene.

Cyclisation of Tetrahydrophenanthrylpropionic Acid (X).—(a) *With hydrogen fluoride.* *β*-(1 : 2 : 3 : 4-Tetrahydro-9-phenanthryl)propionic acid (0·6 g.; Bachmann and Cronyn, *loc. cit.*) was treated with hydrogen fluoride at room temperature for 12 hours. The product, in benzene, was washed with dilute sodium carbonate, and the neutral material was isolated by removal of the benzene. Crystallisation from ethanol gave 3′-*keto*-9 : 10-cyclo*penteno*-1 : 2 : 3 : 4-*tetrahydrophenanthrene* (XII) (0·4 g.) as soft colourless needles, m. p. 179° (Found: C, 86·5; H, 6·9. $C_{17}H_{16}O$ requires C, 86·4; H, 6·8%). When this experiment was repeated on a larger scale, some evidence for the presence of another neutral product, in very small quantity, was obtained. This substance could not, however, be obtained homogeneous.

(b) *With stannic chloride.* The propionic acid (0·5 g.), in dry benzene (10 c.c.), was treated with phosphorus pentachloride (0·4 g.). After an hour, the mixture was warmed on the steam-bath for a few minutes to complete the reaction. This solution of the acid chloride was cooled in ice, and an ice-cold solution of stannic chloride (1 c.c.) in dry benzene (10 c.c.) added. After standing for an hour, in an ice-bath, the dark red complex was decomposed with ice and hydrochloric acid. The benzene solution, after being washed with dilute sodium carbonate, was concentrated, and passed through a column of alumina. Only one product (0·3 g.) was isolated from the eluate, and this formed colourless needles, m. p. 177° (from alcohol) not depressed by admixture with product obtained as in (a).

(c) *With aluminium chloride.* A mixture of the propionic acid (0·5 g.) and thionyl chloride (2 c.c.) in ether was left at room temperature for 2 hours. Ether and excess of thionyl chloride were removed by warming under reduced pressure, and the resulting acid chloride, in nitrobenzene (5 c.c.), was added to an ice-cold mixture of aluminium chloride (1 g.) and nitrobenzene (5 c.c.). After 24 hours at room temperature, the product (0·25 g.) was isolated in the usual way. It formed colourless needles, m. p. 177—179°, from ethanol, and the m. p. was not depressed by admixture with a specimen obtained as above.

9 : 10-cyclo*Penteno*-1 : 2 : 3 : 4-*tetrahydrophenanthrene*.—The above keto*cyclo*pentenotetrahydrophenanthrene (0·7 g.) was heated under reflux with amalgamated zinc (7 g.), concentrated hydrochloric acid (40 c.c.), glacial acetic acid (10 c.c.), and toluene (10 c.c.) for 24 hours. The toluene layer was separated, and the product obtained from this was dissolved in benzene and passed through a column of alumina. A colourless band with a blue fluorescence in ultra-violet light was eluted, and the product obtained from it recrystallised from ethanol. 9 : 10-cyclo*Penteno*-1 : 2 : 3 : 4-*tetrahydrophenanthrene* (0·4 g.) formed colourless needles, m. p. 65—66° (Found: C, 91·9; H, 8·1. $C_{17}H_{18}$ requires C, 91·9; H, 8·1%).

Dehydrogenation of this substance (0·1 g.) with palladium-black (0·02 g.) at 290—300° in an atmosphere of carbon dioxide proceeded smoothly. After sublimation *in vacuo* and recrystallisation from ethanol, 9 : 10-*cyclo*pentenophenanthrene was obtained as long colourless needles, m. p. 149° (lit., m. p. 154°; 149—150°), not depressed on admixture with an authentic specimen of 9 : 10-*cyclo*pentenophenanthrene.

One of us (G. M. B.) has been working with an I.C.I. Research Fellowship and we are also indebted to the University of Glasgow for a grant (to W. C.). The microanalyses were by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

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438. *Experiments on the Synthesis of Rotenone and its Derivatives. Part XVI. The Synthesis of Abutic Acid and its Analogues.*

By G. W. Holton, G. Parker, and Alexander Robertson.

Application of the Perkin transformation to esters of 3-chlorocoumarin-4-carboxylic acids and to their methyl ethers of type (IV), derived from resorcinol, phloroglucinol, and pyrogallol, gave satisfactory yields of the corresponding coumarone-2 : 3-dicarboxylic acids type (VI). By this procedure abutic acid (VIII), a degradation product of rotenononic acid, has been synthesised from 4-hydroxyveratrole.

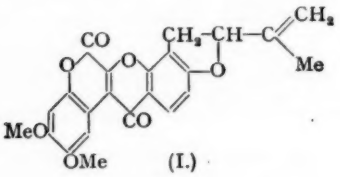
It has also been shown that on being heated with alkali the esters of 3-methoxycoumarin-4-carboxylic acids of type (IX), derived from resorcinol and phloroglucinol, are also readily converted into the corresponding coumarone-2 : 3-dicarboxylic acids, a process which affords a close analogy to the mechanism postulated for the rotenonone–rotenononic acid change (La Forge and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 1091).

When rotenone is oxidised with nitrous acid or chromic acid (Butenandt, *Annalen*, 1928, **464**, 255; Takei, *Biochem. Z.*, 1925, **157**, 1) the group O·CH_2·C< is converted into a lactone system with the formation of the compound rotenonone $C_{23}H_{18}O_7$, for which the structure (I) has been proposed. Under the influence of warm 5% aqueous potassium hydroxide this lactone is hydrolysed and the resulting product (II) subsequently undergoes rearrangement with the formation of rotenononic acid to which the structure (III) has been allocated. The latter formula was deduced from the behaviour of the acid on oxidation with hydrogen peroxide whereby there is formed tubaic acid along with a dibasic acid, abutic acid, for which Takei (*Ber.*, 1932, **65**, 1049) has proposed formula (VIII). In this connection it may be noted that the mechanism postulated for the formation of rotenononic acid from rotenonone finds a close analogy in the well known Perkin transformation of a 3-halogen-substituted coumarin into the corresponding coumarone-2-carboxylic acid (*J.*, 1870, **8**, 368; 1871, **9**, 37), a reaction which has been extensively investigated. As a first step in attempting to confirm the formula proposed for rotenononic acid the synthesis of abutic acid was undertaken and the present communication deals with this topic.

As far as we have been able to learn from the literature, three routes have been employed for the synthesis of coumarone-2 : 3-dicarboxylic acids : (*a*) from isatin (Titanoff *et al.*, *Helv. Chim. Acta*, 1937, **20**, 883; Huntress and Hearson, *J. Amer. Chem. Soc.*, 1941, **63**, 2762), (*b*) by the cyclisation of oxalophenoxyacetate (Koelsch and Whitney, *ibid.*, p. 1762; Huntress and Olsen, *ibid.*, 1948, **70**, 2856), and (*c*) by the application of the Perkin transformation to 3-chloro-4-carbethoxycoumarins (Dey, *J.*, 1915, **107**, 1606), *e.g.*, conversion of type (IV) into type (VI) by way of (V). Although the only examples of procedure (*c*) described by Dey are the transformations of the ethyl 3-chloro-7-methyl- and 6 : 7-dimethyl-coumarin-4-carboxylate into the corresponding coumarone-2 : 3-dicarboxylic acids, this route appeared to us to be a flexible one, especially in the case of derivatives of *m*-dihydroxyphenols where the requisite 3-chlorocoumarins are readily accessible by means of the von Pechmann reaction or a modification of it. Further, it seemed likely that this method would afford a means of preparing hydroxy-derivatives of coumarone-2 : 3-dicarboxylic acids.

Accordingly, in conjunction with the synthesis of abutic acid by this procedure we have also applied the reaction to a series of 3-chlorocoumarins type (IV) derived from resorcinol, phloroglucinol, and pyrogallol. For example, the condensation of resorcinol with ethyl β-chloro-β-carbethoxypyruvate by the alcohol–hydrogen chloride method (modified von Pechmann method) gave an excellent yield of *ethyl 3-chloro-7-hydroxycoumarin-4-carboxylate* (IV; R = H, R′ = Et), which on methylation furnished the *methyl ether* (IV; R = Me; R′ = Et) identical with the product formed directly when resorcinol is replaced by resorcinol monomethyl ether in the von Pechmann reaction. When heated under reflux with 5% aqueous potassium hydroxide the carbethoxycoumarin (IV; R = H, R′ = Et) was almost quantitatively converted into *6-hydroxycoumarone-2 : 3-dicarboxylic acid* (VI; R = R′ = H). When the methyl ether (IV; R = Me, R′ = Et) of this coumarin was warmed with 5% aqueous potassium hydroxide on the steam-bath, the carbethoxy-group was hydrolysed without the Perkin transformation being effected and *3-chloro-7-methoxycoumarin-4-carboxylic acid* (IV; R = Me, R′ = H) was obtained, identical with a specimen prepared by hydrolysis of the ester with boiling 40% sulphuric acid. The structure of this acid was confirmed by its reconversion into the original ethyl ester by the ethyl iodide–silver salt method. When heated under reflux with 10% aqueous potassium hydroxide or with 20% methanolic potassium hydroxide ethyl 3-chloro-7-methoxycoumarin-4-carboxylate was transformed almost quantitatively into *6-methoxycoumarone-2 : 3-dicarboxylic*

acid, identical with the acid prepared by methylation of 6-hydroxycoumarone-2 : 3-dicarboxylic acid with diazomethane and subsequent hydrolysis of the resulting ***methyl 6-methoxycoumarone-2 : 3-dicarboxylate***.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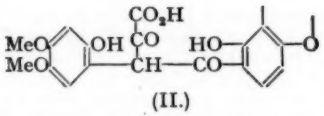
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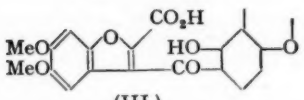
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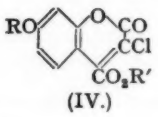
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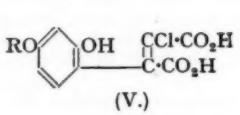
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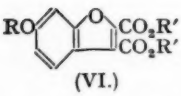
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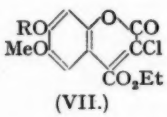
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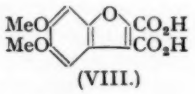
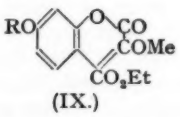

(VIII.)


(IX.)

For the synthesis of abutic acid ***ethyl 3-chloro-7-hydroxy-6-methoxycoumarin-4-carboxylate*** (VII; R = H) was prepared from 2 : 4-dihydroxyanisole by the modified von Pechmann method and on methylation furnished ***ethyl 3-chloro-6 : 7-dimethoxycoumarin-4-carboxylate*** (VII; R = Me), identical with a specimen prepared directly from 4-hydroxyveratrole by the general method. On being boiled with 10% aqueous sodium hydroxide the latter coumarin was converted into abutic acid having properties identical with those of the natural derivative. In this case the yield of the crude conversion product was satisfactory but that of the purified material was considerably reduced owing to losses incurred in removing small amounts of dark impurities.

As a closer analogy to the rotenonone–rotenononic acid change than is afforded by the conversion of 3-chlorocoumarins into the corresponding coumarone-2 : 3-dicarboxylic acids, we have examined the behaviour of 3-methoxycoumarins of type (IX), derived from resorcinol and phloroglucinol, towards warm alkalis. ***Ethyl 7-hydroxy-3-methoxycoumarin-4-carboxylate*** (IX; R = H) has been prepared by the interaction of resorcinol and the sodio-derivative of ***ethyl β-methoxy-β-carbomethoxypyruvate*** in boiling alcohol, and on treatment with boiling methanolic potassium hydroxide is converted into 6-hydroxycoumarone-2 : 3- dicarboxylic acid (VI; R = R′ = H). Likewise the methyl ether (IX; R = Me), which is obtained from the phenol (IX; R = H) by the methyl iodide–potassium carbonate or diazomethane method, gives 6-methoxycoumarone-2 : 3-dicarboxylic acid under similar conditions. Similarly, ***ethyl 3 : 5 : 7-trimethoxycoumarin-4-carboxylate*** was prepared from phloroglucinol dimethyl ether and with hot alkali gave 4 : 6-dimethoxycoumarone-2 : 3-dicarboxylic acid identical with a specimen obtained from the analogous 3-chlorocoumarin. These results serve to support the conclusion of La Forge and Smith (*J. Amer. Chem. Soc.*, 1930, **52**, 1091) regarding the mechanism of the rotenonone–rotenononic acid change and the structure of the resulting rotenononic acid.

Experimental.

Ethyl β-Chloro-β-carbethoxypyruvate.—The following recipe was employed for the preparation of this compound (cf. Wislicenus, *Ber.*, 1910, **43**, 3529). Ethyl chloroacetate (122 g.) was added dropwise in the course of 3 hours to a frequently agitated mixture of ethyl oxalate (146 g.) and ether (400 ml.) containing alcohol-free sodium ethoxide (from 23 g. of sodium) at room temperature. 24 Hours later the yellow sodio-derivative was dissolved in ice-cold water (200 ml.), the mixture was acidified (Congo-red) with dilute hydrochloric acid, the ethereal layer was separated, the residue was extracted with ether (100 ml.), and the combined ethereal solutions were dried and evaporated. Distillation of the product in a vacuum gave the ester as a pale yellow liquid (120 g.), b. p. 139—142°/12 mm. We have found that the preparation of this compound by the chlorination of ethyl oxaloacetate with sulphuryl chloride as described by Peratoner (*Gazzetta*, 1892, **22**, No. 11, 38) is troublesome and gives lower yields of a product which is difficult to purify.

The interaction of pulverised sodium (5·8 g.), methyl oxalate (29·5 g.), and methyl chloroacetate (30 ml., added dropwise with continued stirring) in ether (100 ml.) gave rise to the sodio-derivative of ***methyl β-chloro-β-carbomethoxypyruvate*** in the course of 2 days. Decomposition of this solid by means of dilute acetic acid, followed by isolation with ether, gave the ester (20·5 g.), as a mobile pale yellow oil, b. p. 113—115°/0·3 mm., having a violet-red ferric reaction in alcohol (Found : C, 36·6; H, 3·9; Cl, 18·8. $C_6H_7O_5Cl$ requires C, 37·0; H, 3·6; Cl, 18·3%).

Ethyl β-Carbomethoxy-β-methoxypyruvate.—Methyl methoxyacetate (23 g.) was added dropwise to a mixture of ethyl oxalate (22 ml.) and ether (200 ml.) containing pulverised sodium (4·6 g.), and 2 days later the solvent was distilled off, leaving a product which consisted mainly of the sodio-derivative of *ethyl β-carbomethoxy-β-methoxypyruvate* and was sufficiently pure to be used directly in the preparation of coumarins of type (IX). Treatment of the ethereal reaction mixture with acetic acid (26 g. in 85 ml. of water) and then N-sulphuric acid (120 ml.), followed by extraction of the aqueous layer with a further quantity of ether (100 ml. × 6) and evaporation of the dried extracts, gave the keto-ester which was purified by distillation in a vacuum and obtained as a pale yellow oil (12 g.), b. p. 75—78°/0·05 mm. (Found: C, 47·3; H, 6·0. $C_8H_{12}O_6$ requires C, 47·1; H, 5·9%). This compound gives a violet-red ferric reaction in alcohol, rapidly decolorises aqueous potassium permanganate, readily reduces Fehling's solution and ammoniacal silver nitrate, and forms a green copper complex with copper acetate solution.

Ethyl 3-Chloro-7-hydroxycoumarin-4-carboxylate (IV; R = H, R′ = Et).—A solution of resorcinol (4·6 g.) and ethyl β-chloro-β-carbethoxypyruvate in alcohol (50 ml.) was saturated with hydrogen chloride at room temperature in the course of 2 hours, and 24 hours later the *ethyl 3-chloro-7-hydroxycoumarin-4-carboxylate* was collected, and recrystallised from alcohol or acetic acid, forming pale yellow prisms (7·6 g.), m. p. 234°, insoluble in aqueous sodium hydrogen carbonate and forming a yellow solution in warm aqueous sodium hydroxide [Found: C, 53·9; H, 3·5; Cl, 13·8; *M* (Rast), 267. $C_{12}H_9O_5Cl$ requires C, 53·6; H, 3·4; Cl, 13·2%; *M*, 268]. Methylation of this compound (3 g.) with excess of methyl iodide and potassium carbonate in boiling acetone (50 ml.) during 3 hours gave rise to *ethyl 3-chloro-7-methoxycoumarin-4-carboxylate* which separated from methanol in pale yellow rhombic plates (2·4 g.), m. p. 119°, identical with a specimen prepared in almost quantitative yield by the action of excess of ethereal diazomethane on ethyl 3-chloro-7-hydroxycoumarin-4-carboxylate, and having a negative ferric reaction (Found: C, 55·0; H, 4·0. $C_{13}H_{11}O_5Cl$ requires C, 55·2; H, 3·9%). This compound (0·6 g.) was also prepared by the condensation of ethyl β-chloro-β-carbethoxypyruvate (4·5 g.) and resorcinol monomethyl ether (2·5 g.) in alcohol (25 ml.) with excess of hydrogen chloride during 24 hours and isolated by evaporation of most of the solvent in a vacuum.

When methyl β-chloro-β-carbomethoxypyruvate (3·5 g.) was employed in place of the ethyl ester in the condensation with resorcinol (2 g.) in methanol (10 ml.) saturated with hydrogen chloride, *methyl 3-chloro-7-hydroxycoumarin-4-carboxylate* (IV; R = H, R′ = Me) (2·8 g.) was obtained and on crystallisation from methanol formed elongated yellow prisms, m. p. 212—214°, readily soluble in acetone and moderately soluble in acetic acid (Found: C, 51·8; H, 2·8; Cl, 14·2. $C_{11}H_7O_5Cl$ requires C, 51·9; H, 2·8; Cl, 14·0%). Methylation of this compound (4 g.) in boiling acetone (50 ml.) by the methyl iodide–potassium carbonate method gave *methyl 3-chloro-7-methoxycoumarin-4-carboxylate* (IV; R = Me, R′ = Me) which formed pale greenish-yellow prisms (3 g.), m. p. 152—153°, from a little acetone and then benzene or methanol (Found: C, 53·4; H, 3·3; Cl, 12·7. $C_{12}H_9O_5Cl$ requires C, 53·6; H, 3·3; Cl, 13·2%).

Hydrolysis of ethyl 3-chloro-7-methoxycoumarin-4-carboxylate (1 g.) with boiling sulphuric acid (from 20 ml. of concentrated acid and 50 ml. of water) gave *3-chloro-7-methoxycoumarin-4-carboxylic acid* (IV; R = Me, R′ = H) which was isolated with ether (50 ml. × 5) and separated from unchanged ester (0·3 g.) by means of aqueous sodium hydrogen carbonate. Crystallised from alcohol or acetic acid this acid formed stellate clusters of needles (0·3 g.), m. p. 272° (decomp.; after sintering at 262°) [Found: C, 51·7; H, 3·0; *M* (by titration), 247. $C_{11}H_7O_5Cl$ requires C, 52·0; H, 2·8%; *M*, 254·5]. Esterification of this acid by the silver salt–ethyl iodide method re-formed the carbethoxycoumarin, m. p. and mixed m. p. 119°. Prepared from the acid (1 g.) by means of phosphorus pentachloride (0·85 g.) in chloroform (50 ml.), the acid chloride was treated with aniline, giving rise to the *anilide* which formed colourless rectangular plates (1·1 g.), m. p. 245°, from alcohol or ethyl acetate (Found: C, 61·9; H, 3·7. $C_{17}H_{12}O_4NCl$ requires C, 61·9; H, 3·6%).

6-Hydroxycoumarone-2 : 3-dicarboxylic Acid (VI; R = R′ = H).—A solution of ethyl 3-chloro-7-hydroxycoumarin-4-carboxylate (1·5 g.) in 5% aqueous potassium hydroxide was heated on the steam-bath for 1 hour and on acidification with concentrated hydrochloric acid the filtered red reaction mixture, which had a green fluorescence, gave the *acid* which formed almost colourless needles (1·1 g.), m. p. 277° (decomp.), from dilute hydrochloric acid, acetic acid–hydrochloric acid, or ethyl acetate–light petroleum (b. p. 60—80°) (Found, in specimen dried in a high vacuum at 100°: C, 54·0; H, 3·0. $C_{10}H_6O_6$ requires C, 54·1; H, 2·7%). This acid was also obtained from the corresponding carbomethoxycoumarin (IV; R = H, R′ = Me) by the same procedure.

6-Methoxycoumarone-2 : 3-dicarboxylic Acid (VI; R = Me, R′ = H).—Prepared by the action of boiling 10% aqueous sodium hydroxide (20 ml.) on ethyl 3-chloro-7-methoxycoumarin-4-carboxylate (5 g.) during 40 minutes, this *acid* formed elongated pale yellow needles (3·4 g.), m. p. 219° (decomp.), from warm dilute hydrochloric acid or from a little ethyl acetate [Found: C, 56·0; H, 3·5; equiv. (by titration), 120·1. $C_{11}H_8O_6$ requires C, 55·9; H, 3·4%; equiv., 118]. The acid, which was also formed by the action of boiling 10% aqueous potassium hydroxide on the corresponding carbomethoxycoumarin, was readily soluble in water and in the usual solvents except light petroleum. On esterification with diazomethane the compound gave the *methyl* ester, forming pale yellow needles, m. p. 115°, from ethyl acetate–light petroleum (b. p. 60—80°) and then methanol (Found: C, 59·0; H, 4·5. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·5%).

6-Methoxycoumarone-2 : 3-dicarboxylic acid (2 g.) in chloroform (50 ml.) was treated with thionyl chloride (10 ml.), and 30 minutes later the solvent and excess of thionyl chloride were removed by distillation in a vacuum, leaving the acid chloride as a light-brown solid which reacted with aniline (10 ml.) on the steam-bath to give the *dianilide*. This derivative formed pale yellow needles (2·4 g.), m. p. 192°, from alcohol or dilute acetic acid (Found: N, 7·2. $C_{28}H_{18}O_4N_2$ requires N, 7·3%).

Ethyl 7-Hydroxy-3-methoxycoumarin-4-carboxylate (IX; R = H).—A mixture of resorcinol (80 g.), the sodio-derivative of ethyl β-methoxy-β-carbomethoxypyruvate (from 40 ml. of ester), and alcohol (250 ml.) was heated under reflux for 2 hours, cooled, and poured into dilute sulphuric acid (50 ml. of concentrated sulphuric acid and 2·5 l. of water). Next day the precipitate was collected, washed, and crystallised from dilute alcohol or acetic acid, giving *ethyl 7-hydroxy-3-methoxycoumarin-4-carboxylate* in

elongated plates (26 g.), m. p. 184°, readily soluble in acetone or ethyl acetate and sparingly soluble in benzene (Found: C, 59·3; H, 4·6; OMe, 11·9. $C_{13}H_9O_5 \cdot OMe$ requires C, 59·1; H, 4·5; OMe, 11·7%). Methylation of this compound by means of diazomethane or by the methyl iodide–potassium carbonate method gave *ethyl* 3 : 7-*dimethoxycoumarin*-4-*carboxylate* which separated from light petroleum in colourless prisms, m. p. 83·5—84° (Found: C, 60·2; H, 4·9. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%).

Ethyl 7-hydroxy-3-methoxycoumarin-4-carboxylate (1 g.) was heated under reflux with methanolic potassium hydroxide (from 8 g. of potassium hydroxide, 5 ml. of water, and 35 ml. of methanol) on the steam-bath for 3 hours, and after about half of the methanol had been distilled off the residue was diluted with water (20 ml.), filtered, and acidified with excess of concentrated hydrochloric acid. 6-Hydroxycoumarone-2 : 3-dicarboxylic acid was isolated by extraction of the acidic liquor with ether, and on purification from dilute hydrochloric acid formed needles, m. p. 277°, identical with a specimen obtained from the corresponding 3-chlorocoumarin. Treated with an excess of diazomethane this acid gave methyl 6-methoxycoumarone-2 : 3-dicarboxylate, m. p. 113°, undepressed on admixture with an authentic specimen, m. p. 115°.

When ethyl 3 : 7-dimethoxycoumarin-4-carboxylate (0·5 g.) was heated under reflux with 20% methanolic potassium hydroxide (20 ml.), and part of the alcohol removed by evaporation in a vacuum, the residue on acidification gave 6-methoxycoumarone-2 : 3-dicarboxylic acid (0·3 g.), m. p. and mixed m. p. 217—218°, after purification.

Ethyl 3-*Chloro*-5 : 7-*dihydroxycoumarin*-4-*carboxylate*.—The condensation of anhydrous phloroglucinol (6 g.) and ethyl β-chloro-β-carbethoxypyruvate (12 g.), dissolved in alcohol (45 ml.), with excess of hydrogen chloride in the course of 2 hours gave *ethyl* 3-*chloro*-5 : 7-*dihydroxycoumarin*-4-*carboxylate* which separated from ethyl acetate or acetic acid in pale yellow squat prisms and from aqueous acetone or alcohol in needles (3·75 g.), m. p. 257° (rapid heating) (Found, in a specimen dried in a high vacuum at 80°: C, 50·4; H, 3·3. $C_{12}H_9O_6Cl$ requires C, 50·6; H, 3·2%). The crystal habit of this compound appears to depend somewhat on the solvent used. On being warmed the pale yellow solution of the coumarin in concentrated sulphuric acid becomes cherry-red. When methyl β-chloro-β-carbomethoxypyruvate was employed in place of the ethyl ester, *methyl* 3-*chloro*-5 : 7-*dihydroxycoumarin*-4-*carboxylate* was obtained, forming pale yellow prisms, m. p. 255—258°; yield, 2·5 g. from 2·5 g. of phloroglucinol and 4 g. of ester (Found: C, 59·1; H, 2·5; Cl, 13·0. $C_{11}H_7O_6Cl$ requires C, 48·8; H, 2·6; Cl, 13·1%).

Methylation of ethyl 3-chloro-5 : 7-dihydroxycoumarin-4-carboxylate by the methyl iodide–potassium carbonate method or by means of an excess of diazomethane gave rise to *ethyl* 3-*chloro*-5 : 7-*dimethoxycoumarin*-4-*carboxylate*, forming pale yellow plates, m. p. 155—156°, from ethyl acetate, identical with a specimen prepared by the condensation of phloroglucinol dimethyl ether and ethyl β-chloro-β-carbethoxypyruvate with an excess of alcoholic hydrogen chloride (Found: C, 53·5; H, 4·3; Cl, 11·3. $C_{14}H_{13}O_6Cl$ requires C, 53·8; H, 4·2; Cl, 11·4%). This ester exhibits dimorphism. The unstable form is sometimes obtained by the direct condensation method and may be purified from methanol or alcohol, forming pale yellow needles, m. p. 141—143°, which, on being kept in contact with the solvent or on recrystallisation from benzene, ethyl acetate, or acetone change into the stable form, m. p. 155—156°.

Hydrolysis of ethyl 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylate (2·3 g.) with a boiling mixture of sulphuric acid (100 ml.) and water (100 ml.) for 45 minutes gave 3-*chloro*-5 : 7-*dimethoxycoumarin*-4-*carboxylic acid* which on isolation with ether was obtained as a pale yellow solid (2 g.), readily soluble in water, alcohol or acetone. Recrystallised from ethyl acetate, acetic acid, or methanol this coumarin formed colourless needles (1·8 g.), m. p. 270—272° and decomposing at 277° with effervescence (Found: C, 50·4; H, 3·2; Cl, 12·0. $C_{12}H_9O_6Cl$ requires C, 50·6; H, 3·2; Cl, 12·5%). The hydrolysis of ethyl 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylate with 5% aqueous potassium hydroxide (120 ml.) on the steam-bath for 20 minutes, followed by extraction of the acidified hydrolysate with ether, gave the same acid (1·3 g.), m. p. 270—272°, after purification. Esterification of this acid by the silver salt–ethyl iodide method regenerated the ethyl ester, m. p. 154—155°, undepressed on admixture with an authentic specimen.

Methylation of methyl 3-chloro-5 : 7-dihydroxycoumarin-4-carboxylate with an excess of diazomethane or esterification of 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylic acid with the same reagent gave rise to *methyl* 3-*chloro*-5 : 7-*dimethoxycoumarin*-4-*carboxylate* which formed minute cream-coloured needles, m. p. 171° (Found: C, 51·9; H, 3·7; Cl, 11·8. $C_{13}H_{11}O_6Cl$ requires C, 52·3; H, 3·7; Cl, 11·9%).

4 : 6-*Dimethoxycoumarone*-2 : 3-*dicarboxylic Acid*.—A solution of ethyl 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylate (3 g.) in methanol (50 ml.) was mixed with 20% methanolic potassium hydroxide (25 ml.), the solution was boiled under reflux for 2 hours, and next day about half of the methanol was evaporated off. After the addition of water (50 ml.) the mixture was acidified with hydrochloric acid, and 4 : 6-*dimethoxycoumarone*-2 : 3-*dicarboxylic acid* was isolated with ether and crystallised from ethyl acetate or acetic acid, forming colourless prisms, m. p. 219°, and giving a green fluorescein reaction with resorcinol (Found: C, 54·0; H, 4·0. $C_{12}H_{10}O_7$ requires C, 54·3; H, 3·8%). On warming, the pale yellow colour of the solution of this compound in concentrated sulphuric acid changes to green. The rearrangement of ethyl 3-chloro-5 : 7-dimethoxycoumarin-4-carboxylate was also effected with boiling 10% aqueous potassium hydroxide in the course of 75 minutes. Esterification of 4 : 6-dimethoxycoumarone-2 : 3-dicarboxylic acid (1 g.) with an excess of diazomethane gave the *methyl* ester which formed colourless rectangular prisms (0·85 g.), m. p. 169°, from methanol (Found: C, 57·0; H, 5·0. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%). Hydrolysis of this ester with 15% aqueous sodium hydroxide regenerated the parent acid, m. p. and mixed m. p. 218° after purification.

On being heated with 10% aqueous potassium hydroxide on the steam-bath for 45 minutes ethyl 3-chloro-5 : 7-dihydroxycoumarin-4-carboxylate (3 g.) yielded 4 : 6-dihydroxycoumarone-2 : 3-dicarboxylic acid which was extracted from the cooled acidified reaction mixture with ether. Recrystallised from formic acid this coumarone formed tiny needles, m. p. 252°, and on treatment with excess of diazomethane gave methyl 4 : 6-dimethoxycoumarone-2 : 3-dicarboxylate, m. p. and mixed m. p. 169°.

Ethyl 3 : 5 : 7-*trimethoxycoumarin*-4-*carboxylate* was prepared in poor yield by the condensation of

phloroglucinol dimethyl ether (2·8 g.) and ethyl β-methoxy-β-carbomethoxypyruvate (2 g.) in alcoholic hydrogen chloride. After 8 days the crystalline product (0·4 g.), m. p. 110—120°, which had separated, was collected and the filtrate then diluted with water, neutralised with sodium hydrogen carbonate, and extracted with ether. Evaporation of the combined extracts, followed by crystallisation of the residue from alcohol, gave rosettes of plates (0·4 g.), m. p. 117—120°. Recrystallisation of the combined specimens several times, alternately from alcohol and acetone, gave the *trimethoxy*-ester in tiny clusters of plates, m. p. 131—132° (Found : C, 58·7; H, 5·3. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%). Attempts to improve the yields of this compound by interaction of the sodio-derivative of ethyl β-methoxy-β-carbomethoxypyruvate with phloroglucinol dimethyl ether, and by the condensation of phloroglucinol dimethyl ether and the ester with the aid of ethereal concentrated sulphuric acid or of phosphoric oxide in place of hydrogen chloride in the von Pechmann reaction, were unsuccessful; in each case only minute yields of the required trimethoxycoumarin, m. p. and mixed m. p. 131—132° after purification, were obtained.

When ethyl 3 : 5 : 7-trimethoxycoumarin-4-carboxylate (0·35 g.) was boiled with 20% methanolic potassium hydroxide for 2 hours and the cooled mixture kept for 24 hours, a potassium salt of 4 : 6-dimethoxycoumarone-2 : 3-dicarboxylic acid separated. Decomposition of this compound gave the parent acid, m. p. 217—218°, identified by comparison with an authentic specimen, m. p. 219°.

Ethyl 3-Chloro-7 : 8-dihydroxycoumarin-4-carboxylate.—Prepared from pyrogallol (6 g.) and ethyl β-chloro-β-carbethoxypyruvate (10·6 g.) in alcohol (45 ml.) with excess of hydrogen chloride in the course of 3 days, this *coumarin* separated from acetic acid in clusters of minute prisms (11·5 g.), m. p. 232—234°, readily soluble in alcohol, ethyl acetate, or acetone and giving an olive-green ferric reaction in alcohol which changes to a deep wine-red on the addition of a little alkali (Found : C, 50·9; H, 3·3; Cl, 11·8. $C_{12}H_9O_6Cl$ requires C, 50·6; H, 3·2; Cl, 12·5%). Treatment of the coumarin (3·8 g.), dissolved in ether, with an excess of ethereal diazomethane gave rise to *ethyl 3-chloro-7 : 8-dimethoxycoumarin-4-carboxylate* which formed clusters of needles, m. p. 116—117°, from aqueous acetic acid, benzene, or alcohol (Found : C, 53·6; H, 4·0; Cl, 10·0. $C_{14}H_{13}O_6Cl$ requires C, 53·8; H, 4·2; Cl, 11·4%). This ether was identical with a specimen prepared by methylating the dihydroxycoumarin with methyl iodide and potassium carbonate in boiling acetone.

6 : 7-*Dimethoxycoumarone-2 : 3-dicarboxylic Acid.*—Oxygen-free 10% aqueous potassium hydroxide (120 ml.) was added to ethyl 3-chloro-7 : 8-dihydroxycoumarin-4-carboxylate (3 g.) in an atmosphere of nitrogen, and the mixture heated on the steam-bath for 45 minutes and acidified with concentrated hydrochloric acid. Crystallised from acetone and then from dilute hydrochloric acid, the resulting 6 : 7-*dihydroxycoumarone-2 : 3-dicarboxylic acid* (2 g.) formed pale yellow prisms, m. p. above 300° (Found : C, 50·3; H, 2·7. $C_{10}H_6O_7$ requires C, 50·4; H, 2·5%). Treatment of this acid (2 g.) with an excess of ethereal diazomethane gave *methyl* 6 : 7-*dimethoxycoumarone-2 : 3-dicarboxylate* which separated from methanol, benzene, or aqueous acetone in colourless needles (1·2 g.), m. p. 97° (Found : C, 56·9; H, 4·7. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%).

On being heated under reflux with 10% aqueous potassium hydroxide (50 ml.) for 1·5 hours ethyl 3-chloro-7 : 8-dimethoxycoumarin-4-carboxylate (1·5 g.) gave 6 : 7-*dimethoxycoumarone-2 : 3-dicarboxylic acid* (1·1 g.) which crystallised from ethyl acetate and then acetic acid in yellow needles, m.p. 252° (decomp.), identical with a specimen prepared by the hydrolysis of methyl 6 : 7-dimethoxycoumarone-2 : 3-dicarboxylate (0·2 g.) with boiling 2N-aqueous sodium hydroxide for 20 minutes (Found, in specimen dried in high vacuum at 100° : C, 54·0; H, 3·9. $C_{13}H_{10}O_7$ requires C, 54·1; H, 3·7%).

Ethyl 3-Chloro-6 : 7-dimethoxycoumarin-4-carboxylate (VII; R = Me).—Interaction of 2 : 4-dihydroxyanisole (Head and Robertson, *J.*, 1931, 1241) (2 g.) and ethyl β-chloro-β-carbethoxypyruvate (3 g.) in alcohol (15 ml.) with hydrogen chloride at 0° for 24 hours gave *ethyl 3-chloro-7-hydroxy-6-methoxycoumarin-4-carboxylate* (VII; R = H) which crystallised from acetic acid in pale yellow prisms (0·8 g.), m. p. 220°, soluble in alcohol or acetone and sparingly soluble in ethyl acetate or benzene (Found : C, 52·1; H, 4·0. $C_{13}H_{11}O_6Cl$ requires C, 52·3; H, 3·7%). By the same procedure 4-hydroxyveratrole was converted into *ethyl 3-chloro-6 : 7-dimethoxycoumarin-4-carboxylate* (VII; R = Me) which separated from benzene or ethyl acetate in pale yellow needles, m. p. 174—176° after sintering at 170°, identical in every way with a specimen prepared by the methylation of the foregoing 7-hydroxycoumarin (VII; R = H) with excess of ethereal diazomethane [Found : C, 53·5; H, 4·4; *M* (Rast), 320. $C_{14}H_{13}O_6Cl$ requires C, 53·8; H, 4·2%; *M*, 312].

5 : 6-*Dimethoxycoumarone-2 : 3-dicarboxylic Acid* (*Abutic Acid*) (VIII).—Ethyl 3-chloro-6 : 7-dimethoxycoumarin-4-carboxylate (2 g.) was gently boiled with 10% aqueous sodium hydroxide (40 ml.) for 35 minutes, and the cooled red solution acidified with hydrochloric acid and extracted with ether (50 ml. × 8). The residue left on evaporation of the combined dried extracts was dissolved in the minimum amount of hot water, and the solution boiled for a few minutes with a little charcoal, filtered, and treated with several drops of concentrated hydrochloric acid. When cooled, the filtered liquor deposited abutic acid, m. p. about 242° (decomp.), which was purified from the minimum amount of ethyl acetate and finally obtained in almost colourless prisms (0·3 g.), m. p. 262° (decomp.), identical in every way with the natural compound and giving an intense fluorescein reaction with resorcinol (Found : C, 53·8; H, 3·9. Calc. for $C_{12}H_{10}O_7$: C, 54·1; H, 3·8%). Esterification of this acid with diazomethane gave the *methyl* ester, forming colourless prisms, m. p. 156°, from methanol (Found : C, 57·0; H, 4·9. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%).

Ethyl 3-Chloro-7-methylcoumarin-4-carboxylate.—The ethyl ester of this coumarin (2 g.) was prepared from *m*-cresol (3 g.) and ethyl β-chloro-β-carbethoxypyruvate (6 g.) by the alcoholic hydrogen chloride method and formed colourless needles from acetic acid, m. p. 150°, identical with a specimen prepared by the sulphuric acid procedure, the yield from which was considerably inferior (compare Dey, *J.*, 1915, **107**, 1649, who gives m. p. 154°). On being hydrolysed with a mixture of concentrated sulphuric acid (100 ml.) and water (100 ml.) for 4 hours this ester (3·7 g.) gave the corresponding *3-chloro-7-methylcoumarin-4-carboxylic acid* (2·8 g.), forming colourless needles, m. p. 268—269°, from acetic acid, ethyl acetate, or dilute alcohol (Found : C, 55·5; H, 3·3; Cl, 15·7. $C_{11}H_7O_3Cl$ requires C, 55·4; H, 2·9; Cl, 14·9%). By means of boiling 10% aqueous-alcoholic potassium hydroxide ethyl 3-chloro-7-methylcoumarin-4-

carboxylate was converted into 6-methylcoumarone-2 : 3-dicarboxylic acid, m. p. 231—232° after purification from ethyl acetate; the melting point of the pure compound appears to be somewhat variable, dropping to 220—221° after recrystallisation several times from dilute alcohol, a phenomenon observed by Dey (*loc. cit.*). Esterified with diazomethane the acid gave *methyl 6-methylcoumarone-2 : 3-dicarboxylate*, forming as needles (from methanol), m. p. 64°, soluble in benzene or light petroleum (Found : C, 62·7; H, 4·6. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%).

Ethyl 3-chloro-6-methylcoumarin-4-carboxylate was prepared from *p*-cresol (6 g.) by the alcoholic hydrogen chloride method, forming colourless plates (2·4 g.), m. p. 150° from acetic acid and then alcohol (Found : C, 58·4; H, 4·3. $C_{13}H_{11}O_4Cl$ requires C, 58·5; H, 4·2%). When sulphuric acid or sulphuric acid monohydrate was employed as the condensing agent at 0° for 3 days, there was obtained a second unstable form which, on being crystallised from ether or acetone by slow evaporation of the solvent, formed colourless needles, m. p. 161—162°. Recrystallised from alcohol, this product reverted to the stable form, plates, m. p. and mixed m. p. 148—149°. Hydrolysis of this ester with boiling 50% sulphuric acid during 3·5 hours gave the *coumarin-4-carboxylic acid* which separated from acetic acid in needles, m. p. 282—283°, identical with a specimen obtained when the hydrolysis was effected with 5% aqueous potassium hydroxide on the steam-bath for 45 minutes (Found : C, 55·8; H, 3·2; Cl, 15·0. $C_{11}H_7O_4Cl$ requires C, 55·4; H, 2·9; Cl, 14·9%).

When ethyl 3-chloro-6-methylcoumarin-4-carboxylate (5 g.) was heated under reflux with 10% alcoholic potassium hydroxide (150 ml.) for 2 hours a good yield of *5-methylcoumarone-2 : 3-dicarboxylic acid* was obtained, which formed colourless prisms (4 g.), m. p. 288—290° (decomp.), from dilute hydrochloric acid (Found : C, 60·0; H, 3·7. $C_{11}H_8O_5$ requires C, 60·0; H, 3·6%). Prepared by means of an excess of diazomethane, the *dimethyl* ester of this acid separated from aqueous methanol in needles, m. p. 63—64° (Found : C, 63·0; H, 4·5. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%).

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439. *Syntheses of Glycosides. Part XIV. The Synthesis of Gein and of the Hexa-acetyl β-Vicianoside of (−)-Mandelonitrile believed to be the Hexa-acetate of Vicianin.*

By D. N. CHAUDHURY and ALEXANDER ROBERTSON.

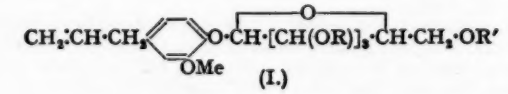
By means of the general method for the synthesis of biosides (Parts VIII and IX) the vicianoside of eugenol has been synthesised and is identical with the natural bioside gein.

The 2 : 3 : 4-triacetyl β-glucoside of (−)-mandelamide was prepared from the β-glucoside of (−)-mandelamide, and on interaction with triacetyl α-(−)-arabinosidyl bromide in the presence of silver oxide gave rise to the hexa-acetyl β-vicianoside of (−)-mandelamide which was dehydrated with phosphoryl chloride to the hexa-acetyl β-vicianoside of (−)-mandelonitrile believed to be the hexa-acetate of vicianin.

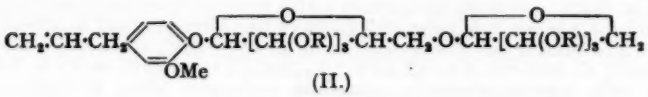
GEIN.

FROM the roots of *Geum urbanum*, Le Bourquelot and Herissey (*Compt. rend.*, 1905, **140**, 870) isolated a glycoside gein which was subsequently shown by Herissey and Cheymol (*ibid.*, 1925, **180**, 384; 1925, **181**, 565; 1926, **183**, 1307) to be a vicianoside (6-L-arabinosido-β-D-glucoside) of eugenol (II; R = H). The structure of this compound has been now confirmed by its synthesis according to the general method (Part VIII, *J.*, 1931, 1881) employed for violutoside (Part IX, *J.*, 1932, 2770), a procedure preferred to the more direct route involving the use of *O*-hexa-acetyl vicianosidyl bromide because of the difficulty in preparing requisite quantities of *O*-hepta-acetyl vicianose (compare McCloskey and Coleman, *J. Amer. Chem. Soc.*, 1943, **65**, 1779) and its bromide.

Attempts to prepare *3-methoxy-4-(tetra-acetyl β-glucosidoxy)-1-allylbenzene* (I; R and R′ = Ac) from eugenol by the convenient silver oxide–quinoline method (Part VI, *J.*, 1930, 2729) gave only intractable brown products owing, presumably, to the presence of the allyl group. The compound was obtained, however, by means of the classical alkali–aqueous acetone procedure in comparatively good yield, and on deacetylation by the ammonia–methanol method gave rise to *3-methoxy-4-β-glucosidoxy-1-allylbenzene* (I; R = R′ = H).



(I.)

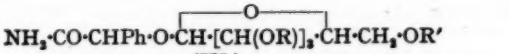


(II.)

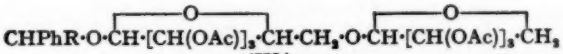
Prepared in the usual manner the derived solid 6-trityl ether (I; R = H, R′ = CPh_3) was not obtained crystalline but on acetylation gave rise to the well crystallised *triacetate* (I; R = Ac, R′ = CPh_3) of the trityl ether, identical with the product prepared directly without the isolation of the intermediate (I; R = H, R′ = CPh_3). Removal of the trityl residue from (I; R = Ac, R′ = CPh_3) in the usual manner furnished *3-methoxy-4-(2′ : 3′ : 4′-triacetyl β-glucosidoxy)-1-allylbenzene* (I; R = Ac, R′ = H), and on interaction with *O*-triacetyl α-L-arabinosidyl bromide in chloroform containing silver oxide and "Drierite" this compound gave a satisfactory yield of *3-methoxy-4-(hexa-acetyl β-vicianosidoxy)-1-allylbenzene* (II; R = Ac). On deacetylation the last acetate furnished the vicianoside (II; R = H) of eugenol, the properties of which are identical with those of gein (*locc. cit.*).

Vicianin.

The bioside vicianin, and analogue of amygdalin, was first isolated from the seeds of *Vicia angustifolia* Roth. by Bertrand (*Compt. rend.*, 1906, **143**, 832) who in collaboration with Weisweiller (*ibid.*, 1908, **147**, 252; 1909, **150**, 180; 1910, **151**, 325, 884) showed that the substance was a β-vicianoside of (−)-mandelonitrile, being hydrolysed by the specific enzyme vicianase to give vicianose. As in the case of gein we preferred to attempt the synthesis of this glycoside by the general stepwise method (Parts VIII and IX, *locc. cit.*) rather than by the direct method involving the use of hexa-acetyl vicianosidyl bromide. For this procedure there are two alternative starting materials, *viz.*, the β-glucoside of (−)-mandelonitrile or the β-glucoside of (−)-mandelamide (III; R = R′ = H). In view of the results of Fischer and Bergmann (*Ber.*, 1917, **50**, 1047) where it is shown that deacetylation of the *O*-tetra-acetyl β-glucoside of (−)-mandelonitrile was accompanied by racemisation of the asymmetric centre in the nitrile residue and that in the separation of the resulting mixture disappointing yields of the pure β-glucoside of (−)-mandelonitrile were obtained, we decided to employ the β-glucoside of (−)-mandelamide as the starting material.



(III.)



(IV.)

Improved yields of the tetra-acetate of ethyl (±)-mandelate β-glucoside facilitated the preparation of the β-glucoside of (±)-mandelamide, from which the requisite β-glucoside of (−)-mandelamide (III; R = R′ = H) was obtained by the Fischer–Bergmann method (*loc. cit.*). Tritylation of the latter glucoside in the usual manner, followed by acetylation of the trityl ether (III; R = H, R′ = CPh_3), which was not isolated, gave the *2 : 3 : 4-triacetyl 6-trityl β-glucoside* of (−)-mandelamide, *i.e.*, (III; R = Ac, R′ = CPh_3), which on removal of the trityl group furnished the *2 : 3 : 4-triacetyl β-glucoside* (III; R = Ac, R′ = H) of (−)-mandelamide in comparatively good yield.

Considerable difficulty was encountered in attempting to attach a 2 : 3 : 4-triacetyl arabinosidyl residue at the 6′-position of (III; R = Ac, R′ = H). Under the usual conditions, *e.g.*, those employed in the case of gein, the product was an intractable gum, and similar material resulted from the application of the modified procedure for the synthesis of alcohol glycosides described by Meystre and Miescher (*Helv. Chim. Acta*, 1944, **27**, 231). Finally, it was found that by carrying out the reaction at 40° small yields of the required *hexa-acetate* of the (−)-mandelamide vicianoside (IV; R = $CO{\cdot}NH_2$) were obtained and on dehydration with phosphoryl chloride this compound yielded the *hexa-acetyl β-vicianoside* (IV; R = CN) of (−)-mandelonitrile. In view of the unsatisfactory yields of (IV; R = CN) which were obtained, the deacetylation of this compound has not been attempted because by analogy with the β-glucoside of (−)-mandelonitrile (Fischer and Bergmann, *loc. cit.*) racemisation of the asymmetric centre of the nitrile residue would be expected to accompany the deacetylation and lead to poor yields of the required isomeride obtained in the separation of the resulting mixture. When a sample of the natural vicianin becomes available, a direct comparison of the foregoing synthetical hexa-acetate will be made with the natural derivative.

Experimental.

3-Methoxy-4-β-glucosidoxy-1-allylbenzene (I; R = R′ = H).—A solution of potassium hydroxide (2·8 g.) in water (50 ml.) was slowly added to eugenol (15 g.) and *O*-tetra-acetyl α-glucosidyl bromide (16 g.) dissolved in acetone (60 ml.), the mixture was kept at room temperature for 16 hours and then extracted

with benzene, and the combined extracts were washed with 2N-aqueous potassium hydroxide (50 ml. × 3 and then with water, dried, and evaporated. Recrystallisation of the residual solid from methanol gave *3-methoxy-4-(tetra-acetyl β-glucosidoxy)-1-allylbenzene* (I; R = R′ = Ac) in colourless rectangular prisms (7 g.), m. p. 123°, $[\alpha]_D^{20}$ −26·0° in chloroform (*c*, 1·0) (Found: C, 58·6; H, 6·4. $C_{34}H_{30}O_{11}$ requires C, 58·3; H, 6·1%). This compound is readily soluble in chloroform or ethyl acetate and moderately soluble in alcohol.

Methanol (500 ml.) containing a suspension of this acetate (18 g.) was saturated at 0° with dry ammonia, the resulting solution was kept at 0° for 6 hours, the solvent and ammonia were removed in a vacuum, and the residue was crystallised from water, giving *3-methoxy-4-β-glucosidoxy-1-allylbenzene* as a *dihydrate* in slender needles (10 g.), m. p. 130—131°, $[\alpha]_D^{20}$ −44·5° in acetone (*c*, 1·0) (Found, in air-dried specimen: C, 53·3; H, 6·8. $C_{16}H_{22}O_7,2H_2O$ requires C, 53·0; H, 7·0%. Found, in material dried in a high vacuum at 110°: C, 58·8; H, 6·7. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·7%).

3-Methoxy-4-(2′ : 3′ : 4′-triacetyl β-glucosidoxy)-1-allylbenzene (I; R = Ac, R_1 = H).—A mixture of anhydrous 3-methoxy-4-β-glucosidoxy-1-allylbenzene (10 g.), triphenylmethyl chloride (9 g.), and absolute pyridine (80 ml.) was warmed on the steam-bath for 1 hour, kept for 36 hours, and then mixed with acetic anhydride (100 ml.). 48 Hours later the solution was poured into ice–water (1·5 l.) which was then vigorously stirred for 2 hours. The resulting granular precipitate was crystallised from methanol, giving *3-methoxy-4-(2′ : 3′ : 4′-triacetyl 6′-trityl β-glucosidoxy)-1-allylbenzene* (I; R = Ac, R′ = CPh_3) in thin glistening plates (15 g.), readily soluble in ethyl acetate, chloroform, benzene, or acetone, and having m. p. 136—137°, $[\alpha]_D^{20}$ +30·0° in chloroform (*c*, 1·0) (Found: C, 71·0; H, 6·2. $C_{41}H_{42}O_{10}$ requires C, 70·9; H, 6·1%).

When a mixture of 3-methoxy-4-β-glucosidoxy-1-allylbenzene (0·8 g.), triphenylmethyl chloride (1 g.), and pyridine (8 ml.) was warmed on the steam-bath for 1 hour and then kept for 3 days, the resulting product obtained by the addition of an excess of ice–water was a gum. Repeated reprecipitation of this material from its methanolic solution by means of ice–water finally gave a flocculent precipitate, but it was not possible to obtain a crystalline product from the latter. On acetylation with acetic anhydride and pyridine the amorphous solid readily gave rise to the well-crystallised 3-methoxy-4-(2′ : 3′ : 4′-triacetyl 6′-trityl β-glucosidoxy)-1-allylbenzene, m. p. 137° (after purification).

A solution of the foregoing trityl ether (15 g.) in acetic acid (40 ml.) at 10° was mixed with a saturated solution of hydrogen bromide in acetic acid (6 ml.) at 0°, and after 1 minute the mixture was rapidly filtered to remove triphenylmethyl bromide, treated with ice–water (300 ml.), and extracted with chloroform. Evaporation of the combined washed and dried extracts left *3-methoxy-4-(2′ : 3′ : 4′-triacetyl β-glucosidoxy)-1-allylbenzene* (I; R = Ac, R′ = H). This was dissolved in the minimum amount of warm chloroform and the solution treated with absolute ether until a faint turbidity appeared. On being kept this mixture deposited the triacetate in prismatic needles (4·5 g.), m. p. 124·5—125°, $[\alpha]_D^{20}$ −22·5° in chloroform (*c*, 0·8), which are readily soluble in alcohol (Found: C, 58·4; H, 6·3. $C_{32}H_{38}O_{10}$ requires C, 58·4; H, 6·2%). Acetylation of this compound (0·1 g.) with acetic anhydride (1 ml.) and sodium acetate (0·5 g.) on the steam-bath for 2 hours regenerated 3-methoxy-4-(tetra-acetyl β-glucosidoxy)-1-allylbenzene, m. p. and mixed m. p. 123°.

3-Methoxy-4-β-vicianosidoxy-1-allylbenzene (*Gein*) (II; R = H).—To ensure success in the following preparation it is essential that all the materials are dry. A mixture of 3-methoxy-4-(2′ : 3′ : 4′-triacetyl β-glucosidoxy)-1-allylbenzene (2·26 g.), " active " silver oxide (1·5 g.), " Drierite " (20 g., which had been heated to 240° for 2 hours), and chloroform (20 ml.) was agitated in a closed flask protected from light for 1 hour. A trace of iodine was then introduced, followed by the gradual addition of a solution of triacetyl α-arabinosidyl bromide (Felton and Freudenberg, *J. Amer. Chem. Soc.*, 1935, **57**, 1638) (1·98 g.) in chloroform (20 ml.) during 1 hour, and the mixture was then stirred for 48 hours and filtered. Evaporation of the filtrate in a vacuum left a viscous syrup which was dissolved in warm methanol (15 ml.) and, on cooling, this solution deposited *3-methoxy-4-(hexa-acetyl β-vicianosidoxy)-1-allylbenzene* (II; R = Ac) in small needles (1·8 g.) which on recrystallisation had m. p. 157—158°, $[\alpha]_D^{20}$ −27·3° in chloroform (*c*, 1·1) (Found: C, 55·7; H, 5·8. $C_{32}H_{44}O_{17}$ requires C, 55·8; H, 5·9%). Deacetylation of this compound (2·5 g.) in methanol (150 ml.), saturated with ammonia at 0°, for 6 hours, gave rise to gein which separated from 95% methanol as a hydrate in masses of felted needles (1·0 g.), m. p. 146—147°, $[\alpha]_D^{20}$ −55·0° in acetone (*c*, 1·0) (Found, in air-dried specimen: C, 53·1; H, 6·9. Calc. for $C_{21}H_{30}O_{11},H_2O$: C, 52·9; H, 6·7%). The properties of the hydrate are identical with those of the natural compound. On being kept in an desiccator over phosphoric oxide this compound lost water of crystallisation, giving the anhydrous glycoside which had m. p. 183—184° (Found, in specimen dried in a high vacuum at 110°: C, 54·9; H, 6·7. Calc. for $C_{21}H_{30}O_{11}$: C, 55·0; H, 6·6%). Acetylation of the glycoside by the acetic anhydride–sodium acetate method re-formed the hexa-acetate, m. p. and mixed m. p. 157—158°.

2 : 3 : 4-*Triacetyl β-Glucoside of* (−)-*Mandelamide* (III; R = Ac, R′ = H).—The following modification of Fischer and Bergmann's method for the preparation of the tetra-acetyl β-glucoside of ethyl (±)-mandelate (*Ber.*, 1917, **50**, 1047) gave improved yields. A mixture of ethyl (±)-mandelate (15 g.), active silver oxide (12 g.), " Drierite " (40 g., which had been heated to 240° for 2 hours), and chloroform (80 ml.) in a flask protected from light was stirred for 1 hour. Iodine (1 g.) was then added to the mixture, followed by a solution of tetra-acetyl α-glucosidyl bromide (23 g.) in chloroform (100 ml.), added dropwise in the course of 1 hour. After having been stirred for 48 hours the reaction mixture was filtered (the solid being washed with chloroform) and the filtrate and washings were evaporated in a vacuum at 15—25 mm. (water-bath at 35°), leaving a viscous syrup from which unchanged ethyl (±)-mandelate was removed by distillation in a vacuum at 160°/0·1—0·2 mm. The almost colourless, very viscous residue was then dissolved in hot alcohol (50 ml.), and on cooling this solution deposited the tetra-acetate of the glucoside in rosettes of colourless needles (16 g.) which had m. p. 102—109° after sintering at 90°. Fischer and Bergmann (*loc. cit.*) record m. p. 102—109°.

The pyridine complex of the β-glucoside of (−)-mandelamide was prepared from the foregoing tetra-acetate according to the method of Fischer and Bergmann (*loc. cit.*) and dried over sulphuric acid in a desiccator. The resulting amorphous product (12 g.) was gently warmed on the steam-bath with pyridine (30 ml.) and triphenylmethyl chloride (12 g.) until a clear solution was formed and, after having

been kept at room temperature for 24 hours, the reaction mixture was treated with acetic anhydride (30 ml.) and, 36 hours later, was poured into ice–water (500 g.). The mixture was agitated for 3 hours, and the resulting viscous product was purified by being dissolved in the minimum amount of warm methanol and reprecipitated with ice–water (300 g.). When this procedure had been repeated three times the crude 2 : 3 : 4-*triacetyl* 6-*trityl* β-*glucoside* (III; R = Ac, R′ = CPh_3) of (−)-mandelamide was obtained as a white amorphous powder which was dried and dissolved in the minimum amount of warm ethyl acetate. Hot light petroleum (b. p. 60—80°) was then added until the solution became slightly turbid; on cooling, the mixture slowly deposited the triacetate of the trityl ether in prismatic needles (13 g.), m. p. 135—136° with slight sintering at 130°, $[\alpha]_D^{20}$ −35·8° in chloroform (*c*, 1·1) (Found: C, 69·0; H, 5·9; N, 1·7. $C_{39}H_{39}O_{10}N$ requires C, 68·7; H, 5·7; N, 2·1%). This compound is readily soluble in methanol, alcohol, or ethyl acetate.

A saturated solution of hydrogen bromide in acetic acid (30 ml.) at 0° was added with stirring to the foregoing triacetate of the trityl ether of (−)-mandelamide (III; R = Ac, R′ = CPh_3) (13 g.), dissolved in acetic acid (30 ml.) at 8°, and after 1 minute the mixture was filtered to remove triphenylmethyl bromide and poured into ice–water (500 g.). The viscous product was isolated by repeated extraction with chloroform, the extracts were well washed, dried, and evaporated in a vacuum, and the residue was dissolved in the minimum amount of hot ethyl acetate. Warm light petroleum (b. p. 60—80°) was then added to this solution until crystalline material began to separate, and on being kept the cooled mixture deposited the 2 : 3 : 4-*triacetyl* β-*glucoside* (III; R = Ac, R′ = H) of (−)-mandelamide in rosettes of feathery needles (6 g.), m. p. 166—167° with slight sintering at 162° after recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°), $[\alpha]_D^{20}$ −90·0° in chloroform (*c*, 1·0) (Found: C, 54·6; H, 5·8; N, 3·2. $C_{20}H_{25}O_{10}N$ requires C, 54·7; H, 5·7; N, 3·2%). Acetylation of this compound with a warm mixture of acetic anhydride and pyridine gave the tetra-acetyl β-glucoside of (−)-mandelamide, identified by comparison with an authentic specimen (Fischer and Bergmann, *loc. cit.*).

Hexa-acetyl β-*Vicianoside of* (−)-*Mandelamide* (IV; R = $CO{\cdot}NH_2$).—A mixture of the foregoing triacetate (III; R = Ac, R′ = H) (1 g.), "active" silver oxide (3 g.), "Drierite" (20 g.), and chloroform (30 ml.), maintained at 40°, was stirred for 1 hour and then treated with a trace of iodine, followed by a solution of triacetyl α-L-arabinosidyl bromide (1 g.) in chloroform (15 ml.) which was added gradually in the course of 1 hour. The mixture was maintained at 40° for a further 8 hours and then at room temperature for 16 hours with continuous agitation, filtered to remove silver salts (which were washed with chloroform), and evaporated in a vacuum. A solution of the residue in a little methanol was poured into ice–water (200 g.), and the resulting precipitate collected, washed, dried, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), giving the *hexa-acetyl* β-*vicianoside* of (−)-mandelamide in small colourless needles (0·2 g.), which had m. p. 189—190°, $[\alpha]_D^{20}$ −65·0° in chloroform (*c*, 1·0) after having been twice recrystallised from the mixed solvent (Found: C, 53·6; H, 5·5; N, 2·2. $C_{31}H_{39}O_{17}N$ requires C, 53·4; H, 5·6; N, 2·0%).

Hexa-acetyl β-*Vicianoside of* (−)-*Mandelonitrile* (IV; R = CN).—The foregoing amide (0·15 g.) was treated with phosphoryl chloride (0·7 g.) at 68—70° for 15 minutes, the excess of chloride was removed in a vacuum, and the residue was triturated with ice–water. Crystallisation of the resulting semi-solid product from methanol gave the *hexa-acetyl* β-*vicianoside* of (−)-mandelonitrile in prismatic needles, m. p. 165° (Found: C, 54·6; H, 5·6. $C_{31}H_{37}O_{16}N$ requires C, 54·8; H, 5·5%).

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440. *Furano-compounds. Part X.* α-*Acylcoumarones and a New Synthesis of* 6-*Hydroxy*-2-iso*propylcoumaran.*

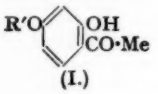
By J. B. D. MACKENZIE, ALEXANDER ROBERTSON, and (in part) ANIS BUSHRA and R. TOWERS.

The application of the Hoesch reaction to 6-hydroxy-3-methylcoumarone with methyl, phenyl, and *p*-methoxyphenyl cyanide has been shown to give 6-hydroxy-2-acyl-3-methylcoumarones, type (III), the orientations of which have been confirmed by independent syntheses.

Interaction of ethyl 6-benzyloxycoumarone-2-carboxylate and methylmagnesium iodide gave rise to 6-benzyloxy-2-(1-hydroxy*iso*propyl)coumarone (IX) whilst with an excess of the latter reagent 6-benzyloxy-2-acetylcoumarone furnished 6-benzyloxy-2-*iso*propenylcoumarone (X) which on simultaneous hydrogenation and debenzylation yielded 6-hydroxy-2-*iso*propylcoumaran (XI; R′ = R″ = H). Prepared in a similar manner 6-methoxy-3-methyl-2-*iso*propenylcoumarone formed an adduct with maleic anhydride and on hydrogenation gave 6-methoxy-3-methyl-2-*iso*propylcoumaran (XI; R′ = R″ = Me).

By analogy with the established behaviour of 3-methyl- and hydroxy-3-methyl-coumarones, type (IV) (*J.*, 1938, 306; 1939, 92, 1594; 1948, 2254), in invariably forming α-formyl derivatives in the Gattermann aldehyde synthesis it appeared likely that the application of the Hoesch reaction to these coumarones would result in the formation of the α-acyl derivatives, type (III, R″ = Alkyl or Aryl). It therefore, seemed of interest to examine the products of the latter reaction more especially in view of the claims of Karrer *et al.* (*Helv. Chim. Acta*, 1919, **2**, 454; 1921, **4**, 718) to have prepared 5-acyl derivatives, type (V), by the condensation of 6-

hydroxy-3-methylcoumarone with phenyl and *p*-methoxyphenyl cyanide. To the ketones, type (V), the Swiss workers have applied the name depsenone.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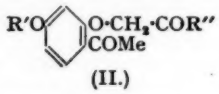
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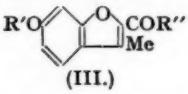
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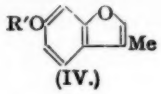
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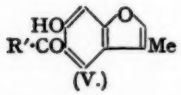
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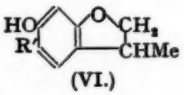
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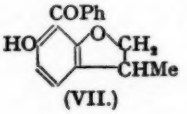
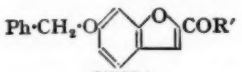

(VII.)

The condensation of methyl cyanide with 6-hydroxy-3-methylcoumarone (IV; R′ = H) by Hoesch's method gave only one product, 6-*hydroxy*-2-*acetyl*-3-*methylcoumarone* (III; R′ = H, R″ = Me) which did not give a ferric reaction in alcohol and on methylation furnished 6-*methoxy*-2-*acetyl*-3-*methylcoumarone* (III; R′ = R″ = Me), identical with the ketone obtained when (IV; R′ = H) was replaced by (IV; R′ = Me) in the Hoesch reaction and when acetyl chloride was allowed to react with (IV; R′ = Me) according to the Friedel–Crafts method with stannic chloride as the condensing agent. The failure of the Hoesch reaction product from (IV; R′ = H) to give a ferric reaction clearly excluded the possibility of the compound being an *o*-hydroxy-ketone, type (V; R′ = Me). The orientation now alloted to the Hoesch product (III; R′ = H, R″ = Me) was confirmed by an independent synthesis of the ether (III; R′ = R″ = Me), *viz.* the interaction of (I; R′ = Me) with chloroacetone in boiling acetone containing potassium carbonate which was accompanied by the cyclisation of the initial reaction product (II; R′ = R″ = Me), giving rise to 6-methoxy-2-acetyl-3-methylcoumarone (III; R′ = R″ = Me) identical with the product prepared directly from (IV; R′ = Me). By the same procedure it has been shown that the condensation product, m. p. 159°, from phenyl cyanide and 6-hydroxy-3-methylcoumarone is 6-*hydroxy*-2-*benzoyl*-3-*methylcoumarone* (III; R′ = H, R″ = Ph) and not 6-hydroxy-5-benzoyl-3-methylcoumarone (V; R′ = Ph) as claimed by Karrer *et al.* (*loc. cit.*). The benzyl ether of the Hoesch reaction product was identical with a specimen synthesised by the interaction of (I; R′ = Ph·CH_2) and ω-bromoacetophenone in boiling acetone containing potassium carbonate with simultaneous cyclisation of the intermediate (II; R′ = Ph·CH_2, R″ = Ph). Debenzylation of the ether prepared by the latter route gave (III; R′ = H, R″ = Ph) identical with the compound prepared by Hoesch's method. The corresponding *methyl ether* has the formula (III; R′ = Me, R″ = Ph). Attempts to condense phenyl cyanide with 6-hydroxy-3-methylcoumaran (VI; R′ = H) by the Hoesch method gave negative results but the interaction of the coumaran with benzoyl chloride according to the Friedel–Crafts procedure gave rise to a ketone, m. p. 172°, which has an intense red ferric reaction in alcohol and is either 6-hydroxy-5-benzoyl- (VI; R′ = Ph·CO) or 6-hydroxy-7-benzoyl-3-methylcoumaran (VII). With regard to the orientation of this compound, m. p. 172°, it may be noted that Kostanecki *et al.* (*Ber.*, 1907, **40**, 3660; 1908, **41**, 1327, 1330) concluded on general grounds that the condensation of coumaran and of 6-methoxy-3-methylcoumaran with aroyl chlorides gave products, type (VI; R′ = Ph·CO), but the absolute orientation of their compounds was not undertaken. We therefore, provisionally assign structure (VI; R′ = Ph·CO) to the *o*-hydroxybenzoyl-3-methylcoumaran obtained from (VI; R′ = H). In view of the fact that the application of the Fries reaction to 6-acetoxy-2-*iso*propylcoumaran gave 6-hydroxy-7-acetyl-2-*iso*propylcoumaran (Part V, *J.*, 1939, 933) we do not regard the orientation (VII) for the benzoylcoumaran as being entirely excluded. Karrer *et al.* (*loc. cit.*) claimed to have prepared 6-hydroxy-5-benzoyl-3-methylcoumaran, m. p. 159°, from 6-hydroxy-3-methylcoumaran and phenyl cyanide by Hoesch's method but, since it would appear that their starting material was mainly 6-hydroxy-3-methylcoumarone (IV; R′ = H) (Part VIII, *loc. cit.*), it seems likely that the substance stated to melt at 159° was in fact mainly, if not entirely, 6-hydroxy-2-benzoyl-3-methylcoumarone, which we have found to melt at 158°.

In agreement with the foregoing results it has also been shown that when phenyl cyanide is replaced by *p*-methoxyphenyl cyanide in the Hoesch reaction applied to 6-hydroxy-3-methylcoumarone the product is 6-*hydroxy*-2-p-*methoxybenzoyl*-3-*methylcoumarone* (III; R′ = H, R″ = C_6H_4·OMe), m. p. 177°, and not 6-hydroxy-5-*p*-methoxybenzoyl-3-methylcoumarone (cf. Karrer *et al.*, *loc. cit.*). The authentic specimen of (III; R′ = H, R″ = C_6H_4·OMe) was prepared by the interaction of 4-*o*-benzylresacetophenone with ω-bromoacetylanisole and

subsequent debenzylation of the resulting 6-*benzyloxy*-2-p-*methoxybenzoyl*-3-*methylcoumarone* (III; R′ = Ph·CH$_2$, R″ = C$_6$H$_4$·OMe).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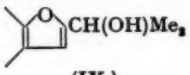
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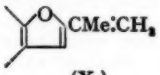
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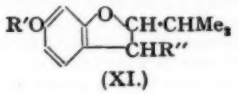
(XI.)

The interaction of two molecular proportions of methylmagnesium iodide with *ethyl* 6-*benzyloxycoumarone*-2-*carboxylate* (VIII; R′ = OEt) gave rise to 6-*benzyloxy*-2-(1-*hydroxy*iso*propyl*)*coumarone* (IX), but when the ester (VIII; R′ = OEt) was replaced by the ketone (VIII, R′ = Me) and an excess of the Grignard reagent employed 6-*benzyloxy*-2-iso*propenyl*-*coumarone* (X) was obtained. Hydrogenation of the latter compound with a palladium–charcoal catalyst was accompanied by debenzylation, giving 6-hydroxy-2-*iso*propylcoumaran (XI; R′ = R″ = H), identical with an authentic sample. This preparation of (XI; R = R″ = H), which is more convenient than the earlier procedure described in Part V (*loc. cit.*), affords additional confirmatory evidence for the structure of euparin (Part V) and of the isomeric 6-hydroxy-2 : 2-dimethylchroman (*J.*, 1937, 1542). In the course of exploratory experiments the synthesis of 6-*methoxy*-3-*methyl*-2-iso*propylcoumaran* (XI; R′ = R″ = Me) was effected by way of 6-*methoxy*-3-*methyl*-2-iso*propenylcoumarone* by the action of an excess of methylmagnesium iodide on ethyl 6-methoxy-3-methylcoumaronecarboxylate followed by hydrogenation of the resulting *iso*propenyl derivative. The latter compound reacted with maleic anhydride to give an adduct.

Experimental.

6-*Methoxy*-2-*acetyl*-3-*methylcoumarone* (III; R′ = R″ = Me).—(*A*) Interaction of 6-methoxy-3-methylcoumarone (5 g.), methyl cyanide (5 ml.), and zinc chloride (3 g.) in ether (100 ml.) saturated with hydrogen chloride during 2 days gave a greenish product which was well washed with ether and dissolved in water (100 ml.). This solution was almost neutralised with ammonia, and then heated on the steam-bath for 15 minutes, giving a yellow solid from which 6-*methoxy*-2-*acetyl*-3-*methylcoumarone* was extracted with boiling light petroleum (b. p. 40—60°) (200 ml.) and then recrystallised from dilute alcohol, forming colourless prisms (4 g.), m. p. 77°, readily soluble in alcohol, benzene, or ether (Found : C, 70·3; H, 5·7; *M*, 215. C$_{12}$H$_{12}$O$_3$ requires C, 70·6; H, 5·9%; *M*, 204). On being warmed the yellow-green solution of the ketone in concentrated sulphuric acid became red and then violet. The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid in crimson needles, m. p. 260° (Found : N, 14·6. C$_{18}$H$_{16}$O$_6$N$_4$ requires N, 14·6%).

(*B*) Acetyl chloride (2·5 g.) was added dropwise to a well stirred mixture of 6-methoxy-3-methylcoumarone (5 g.), stannic chloride (5 g.), and carbon disulphide (70 ml.) maintained at 0°. After having been kept at room temperature for one hour the mixture was decomposed with ice (200 g.), treated with sodium carbonate to neutralise the greater part of the hydrochloric acid, warmed on the steam-bath for ½ hour, and mixed with dilute hydrochloric acid (50 ml.). The carbon disulphide layer was subsequently combined with ethereal extracts of the aqueous liquor and the mixture washed with dilute hydrochloric acid and then aqueous sodium hydrogen carbonate, dried, and evaporated. Distillation of the residue in a vacuum gave 6-methoxy-2-acetyl-3-methylcoumarone which formed prisms (3·4 g.), m. p. and mixed m. p. 77°, from dilute alcohol.

(*C*) A mixture of 4-*O*-methylresacetophenone (20 g.), chloroacetone (18 g.), potassium carbonate (30 g.), and acetone (150 ml.) was refluxed for 15 hours with the addition of more chloroacetone (9 g.) and carbonate (10 g.) after 10 hours. The product was extracted with boiling light petroleum (b. p. 60—80°), the extracts were evaporated, and the residue (21 g.) was heated under reflux (oil-bath at 160°) with acetic anhydride (140 ml.) and sodium acetate (48 g.) for ½ hour and poured into water (800 ml.). 4 Days later extraction of the resulting dark viscous semi-solid with light petroleum (b. p. 60—80°) gave 6-methoxy-2-acetyl-3-methylcoumarone, m. p. and mixed m. p. 77°, after recrystallisation from dilute alcohol.

6-*Hydroxy*-2-*acetyl*-3-*methylcoumarone* (III; R′ = H, R″ = Me).—A solution of 6-hydroxy-3-methylcoumarone (1 g.) and methyl cyanide (2 ml.) in ether (100 ml.) was slowly saturated with hydrogen chloride at room temperature, and next day the semi-solid product was well washed with ether and dissolved in water (150 ml.). After having been treated with ammonia until only faintly acid to Congo-red this solution was heated on the steam-bath for 20 minutes and next day the resulting 6-*hydroxy*-2-*acetyl*-3-*methyl*-*coumarone* was collected, well washed, dried, and crystallised from toluene and then dilute alcohol, forming faintly yellow flat parallelograms (0·7 g.), m. p. 172—173° (Found : C, 69·5; H 5·6. C$_{11}$H$_{10}$O$_3$ requires C, 69·5; H, 5·8%). This ketone, which is easily soluble in ethyl acetate or alcohol and sparingly soluble in carbon tetrachloride or light petroleum, did not give a ferric reaction in alcohol. On being warmed the green solution of the compound in sulphuric acid became red and then purple. The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid in crimson needles, m. p. 283° (decomp.) (Found : N, 15·0. C$_{17}$H$_{14}$O$_6$N$_4$ requires N, 15·1%).

Methylation of the foregoing keto-coumarone (0·5 g.) with methyl iodide (1 ml.) and potassium carbonate (2 g.) in boiling acetone (50 ml.) for 3 hours gave rise to 6-methoxy-2-acetyl-3-methylcoumarone (III; R′ = R″ = Me) which formed prisms (0·4 g.), m. p. 77°, from dilute alcohol and was identical in every way with the authentic specimen. The 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 260° (decomp.) and the *semicarbazone* formed colourless rectangular plates, m. p. 269°, from

methanol, identical with a specimen prepared from the authentic ketone (Found : N, 16·2. $C_{13}H_{15}O_3N_3$ requires N, 16·1%).

2-(6'-Methoxy-3'-methylcoumaron-2'-yl)benzopyrylium Chloride.—Condensation of salicylaldehyde (0·6 g.) and 6-methoxy-2-acetyl-3-methylcoumarone (0·5 g.) in ethyl acetate (15 ml.) with an excess of hydrogen chloride followed by the addition of ether (50 ml.) next day gave the *chloride* which was collected, washed with ether, and crystallised from 1% hydrochloric acid, forming tiny amethyst prisms (0·3 g.) (Found : C, 70·0; H, 4·8; Cl, 10·4. $C_{19}H_{15}O_3Cl$ requires C, 69·8; H, 4·6; Cl, 10·9%). The *perchlorate* separated from acetic acid in elongated slender purple needles having a violet reflex and forming a deep red solution in alcohol which became colourless on the addition of aqueous sodium acetate (Found : C, 58·0; H, 3·9. $C_{19}H_{15}O_7Cl$ requires C, 58·4; H, 3·7%).

In a similar manner *8-methoxy-2-(6'-methoxy-3'-methylcoumaron-2'-yl)benzopyrylium chloride* was prepared from the ketocoumarone (0·5 g.) and *o*-vanillin (0·7 g.) and on crystallisation from 5% hydrochloric acid was obtained in slender violet prisms (0·3 g.), having a copper reflex (Found : C, 67·0; H, 5·0; Cl, 10·6. $C_{20}H_{17}O_4Cl$ requires C, 67·3; H, 4·8; Cl, 10·0%). The perchlorate formed slender red prisms from acetic acid.

6-Hydroxy-2-benzoyl-3-methylcoumarone (III; R' = H, R'' = Ph).—This compound, m. p. 158—159°, was prepared from 6-hydroxy-3-methylcoumarone by Hoesch's method as described by Karrer and Widmer (*loc. cit.*), and on benzylation by means of an excess of benzyl bromide and potassium carbonate gave the *6-benzyloxy-2-benzoyl-3-methylcoumarone* (III, R' = Ph·CH_2, R'' = Ph), m. p. 77°, identical in every way with an authentic specimen prepared by the following procedure. A mixture of 4-*O*-benzylresacetophenone (Gulati *et al.*, *J.*, 1934, 1765) (5 g.), ω-bromoacetophenone (6 g.), potassium carbonate (15 g.), and acetone (120 ml.) was heated under reflux for 20 hours, and on isolation the benzyl ether crystallised from alcohol in rosettes of colourless needles (4 g.), m. p. 77° (Found : C, 80·5; H, 5·4. $C_{23}H_{18}O_3$ requires C, 80·7; H, 5·3%). The 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 250°, from nitrobenzene–alcohol (Found : N, 10·6. $C_{29}H_{22}O_6N_4$ requires N, 10·7%).

An authentic specimen of 6-benzyloxy-2-benzoyl-3-methylcoumarone was debenzylated by being heated under reflux with a mixture of equal volumes of acetic acid and concentrated hydrochloric acid for one hour, the benzyl chloride was removed with a current of steam, and the resulting 6-hydroxy-2-benzoyl-3-methylcoumarone was isolated from the residual liquor by means of ether and purified from non-phenolic material by means of dilute aqueous sodium hydroxide. Crystallised from ligroin, the hydroxy-coumarone formed yellow prisms, m. p. and mixed m. p. 158—159°, identical with a specimen prepared by Hoesch's method.

Methylation of 6-hydroxy-2-benzoyl-3-methylcoumarone by the methyl iodide–potassium carbonate method or by the methyl sulphate method gave *6-methoxy-2-benzoyl-3-methylcoumarone* which was purified by distillation in a high vacuum and then by crystallisation from methanol, forming colourless prisms, m. p. 76° (Found : 76·5; H, 5·1. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%).

6-Hydroxy-5-benzoyl-3-methylcoumaran (VI).—Aluminium chloride (5·5 g.) was added in small portions to a well stirred mixture of 6-hydroxy-3-methylcoumaran (Part VII, *loc. cit.*) (2 g.), nitrobenzene (50 ml.), and benzoyl chloride (3·5 g.) in the course of 10 minutes. The stirring was stopped after 2 hours and 48 hours later the mixture was poured on ice, the product and nitrobenzene were extracted with ether, the combined extracts were evaporated, the nitrobenzene was removed with a current of steam, the residual liquor was cooled, and the crystalline product was isolated by filtration. Recrystallised from alcohol, the resulting *6-hydroxy-5-benzoyl-3-methylcoumaran* formed almost colourless needles, m. p. 172°, which gave an intense red ferric reaction in alcohol (Found : C, 75·7; H, 5·7. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

6-Hydroxy-2-p-methoxybenzoyl-3-methylcoumarone (III; R' = H, R'' = C_6H_4·OMe).—The interaction between 4-*O*-benzylresacetophenone (4 g.), ω-bromoacetylanisole (Kunckel and Scheven, *Ber.*, 1898, **31**, 173) (5 g.), and potassium carbonate (15 g.) in boiling acetone was complete in 3 hours; a test portion did not then give a ferric reaction. On isolation the resulting *6-benzyloxy-2-p-methoxybenzoyl-3-methylcoumarone* crystallised from benzene and then ethyl acetate in almost colourless prisms (3·5 g.), m. p. 160—161°, nearly insoluble in alcohol, sparingly soluble in chloroform, and having a vermilion sulphuric acid reaction changing to crimson when the mixture was warmed (Found : C, 77·3; H, 5·5. $C_{24}H_{20}O_4$ requires C, 77·4; H, 5·4%). The 2 : 4-*dinitrophenylhydrazone* formed crimson rectangular plates, m. p. 232°, from ethyl acetate (Found : N, 10·4. $C_{30}H_{24}O_7N_4$ requires N, 10·1%).

A solution of the foregoing benzyl ether (1 g.) in acetic acid (20 ml.) and concentrated hydrochloric acid (15 ml.) was boiled for an hour, the benzyl chloride was removed with steam, and the resulting *6-hydroxy-2-p-methoxybenzoyl-3-methylcoumarone* was isolated with ether and purified by means of dilute aqueous sodium hydroxide. Crystallised from chloroform, the hydroxy-ketone was obtained in pale yellow plates (0·4 g.), m. p. 177—178°, which formed a deep yellow solution with aqueous sodium hydroxide and had a negative ferric reaction in alcohol (Found : C, 72·6; H, 5·1. $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%). Methylation of this compound (1 g.) by the methyl iodide–potassium carbonate method gave *6-methoxy-2-p-methoxybenzoyl-3-methylcoumarone* which formed colourless plates (0·65 g.), m. p. 142°, from alcohol, having a scarlet-red sulphuric acid reaction (Found : C, 73·1; H, 5·6. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

The foregoing hydroxy-ketone was identical with a specimen prepared by means of the Hoesch reaction as follows. A solution of 6-hydroxy-3-methylcoumarone (1 g.) and *p*-methoxyphenyl cyanide (1·2 g.) in ether (150 ml.) containing zinc chloride (2 g.) was saturated with hydrogen chloride at room temperature. Next day the passage of hydrogen chloride was continued for 2 hours and 24 hours later the mixture was treated with ether (150 ml.), the solvent was decanted, and the residual greenish semi-solid was well washed with fresh solvent and dissolved in water (150 ml.). This acidic solution was almost neutralised with aqueous sodium hydrogen carbonate and then heated on the steam-bath for ½ hour, giving a yellow precipitate of 6-hydroxy-2-*p*-methoxybenzoyl-3-methylcoumarone which was purified from non-phenolic material by means of dilute aqueous sodium hydroxide. A hot ethyl acetate extract (30 ml.) of the product was diluted with light petroleum (b. p. 80—100°) (20 ml.), boiled with charcoal, filtered, and evaporated. Crystallisation of the residue from ethyl acetate gave the hydroxy-

ketone in rosettes of pale yellow needles (0·25 g.), m. p. 177°, identical with an authentic specimen (compare Karrer *et al.*, *loc. cit.*). Methylation of this material gave 6-methoxy-2-*p*-methoxybenzoyl-3-methylcoumarone, m. p. and mixed m. p. 142° (Found: C, 72·9; H, 5·5%).

6-*Benzyloxy*-2-(1-*hydroxy*iso*propyl*)*coumarone* (IX).—A solution of ethyl 6-benzyloxycoumarone-2-carboxylate (Part VII, *J.*, 1948, 2254) (4 g.) in ether (250 ml.) was gradually added to well stirred methylmagnesium iodide (from 0·75 g. of magnesium and 3 g. of methyl iodide) in ether (25 ml.) cooled with ice-water, and the yellow solution heated under reflux on the steam-bath for 20 minutes, cooled, and treated with dilute hydrochloric acid. The ethereal layer was separated, washed with aqueous sodium hydrogen carbonate, dried, and evaporated, and the residue crystallised from dilute alcohol, giving 6-*benzyloxy*-2-(1-*hydroxy*iso*propyl*)*coumarone* (2·5 g.) in long colourless needles, m. p. 74°, readily soluble in alcohol, benzene, or ethyl acetate and sparingly soluble in light petroleum (Found: C, 76·8; H, 6·5; *M*, 290. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%; *M*, 282).

6-*Benzyloxy*-2-*acetylcoumarone* (VIII; R′ = Me).—A mixture of 4-*O*-benzyl-β-resorcylaldehyde (10 g.), potassium hydroxide (2·5 g.), alcohol (60 ml.), and chloroacetone (4·5 g.) was heated under reflux for ½ hour, and, after the addition of water (100 ml.), the greater part of the alcohol was evaporated and the cooled residue extracted with ether. Evaporation of the solvent from the dried extracts left the *ketone* (VIII; R′ = Me) which was purified by distillation in a vacuum, b. p. 130°/0·01 mm., and then by crystallisation from dilute alcohol, forming colourless plates (7·5 g.), m. p. 98°, readily soluble in benzene or ethyl acetate (Found: C, 76·4; H, 5·4. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in scarlet needles, m. p. 248° (Found: N, 12·7. $C_{23}H_{18}O_6N_4$ requires N, 12·6%).

6-*Hydroxy*-2-iso*propyl*coumaran (XI; R′ = R″ = H).—A solution of the foregoing ketone (4 g.) in ether (100 ml.) was slowly added to ethereal methyl magnesium iodide (from 1·5 g. of magnesium, 8 g. of methyl iodide, and 100 ml. of ether) cooled with ice-water, and the mixture was heated on the steam-bath for ½ hour. On isolation the product was distilled in a high vacuum, b. p. 160°/0·004 mm., and then crystallised from alcohol giving 6-*benzyloxy*-2-iso*propenylcoumarone* (X) in colourless plates (1·5 g.), m. p. 91—92°, soluble in benzene or ethyl acetate (Found: C, 81·9; H, 6·3. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%). Hydrogenation of this diene (0·5 g.), dissolved in methanol (100 ml.), with hydrogen and a palladium–charcoal catalyst (from 0·1 g. of palladium chloride and 1 g. of charcoal) gave rise to 6-hydroxy-2-*iso*propylcoumaran which was purified by distillation in a vacuum, b. p. 105°/0·03 mm., and then by crystallisation from light petroleum (b. p. 60—80°), forming colourless rhombic prisms (0·3 g.), m. p. 79°, identical in every way with the specimen described in Part V (*J.*, 1939, 933).

6-*Methoxy*-3-*methyl*-2-iso*propylcoumaran* (XI; R′ = R″ = Me).—Interaction of ethyl 6-methoxy-3-methylcoumarone-2-carboxylate (5 g.) in ether (200 ml.) with methylmagnesium iodide (from 1·5 g. of magnesium, and 5 g. of methyl iodide) at 0° and then by heating under reflux for 45 minutes, and decomposition of the reaction product with dilute hydrochloric acid gave rise to 6-*methoxy*-3-*methyl*-2-iso*propenylcoumarone*. Purified by distillation in a vacuum and then by crystallisation from light petroleum (b. p. 40 —60°), the compound formed irregular prisms (3·2 g.), m. p. 69°, soluble in alcohol or benzene (Found: C, 77·1; H, 6·8. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%). On being heated with maleic anhydride (1 g.) in benzene (2·5 ml.) for 16 hours this (0·5 g.) gave an adduct which was purified by sublimation in a vacuum and then by crystallisation from ethyl acetate–light petroleum (b. p. 80—100°), forming colourless prisms, m. p. 147—148°.

Hydrogenation of 6-methoxy-3-methyl-2-*iso*propenylcoumarone (1·5 g.), dissolved in methanol (100 ml.), with hydrogen and a palladium–charcoal catalyst (from 0·1 g. of palladium chloride and 1 g. of charcoal) was complete in one hour. On isolation 6-*methoxy*-3-*methyl*-2-iso*propylcoumaran* (XI; R′ = R″ = Me) was obtained as a colourless viscous oil (0·4 g.), b. p. 85°/0·05 mm. (Found: C, 75·9; H, 8·9. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%).

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441. *The Chemistry of the Melanins. Part II. The Synthesis of 5:6-Dihydroxyindole-2-carboxylic Acid and Related Compounds.*

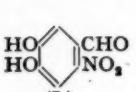
By R. J. S. BEER, L. MCGRATH, ALEXANDER ROBERTSON, and A. B. WOODIER.

In continuation of studies on melanin and its precursors the syntheses of 5:6-dihydroxyindole-2-carboxylic acid, 6:7-dihydroxy-1:2:3:4-tetrahydrocarbazole, and of 5:6-dihydroxy-3-phenyl-, 5:6-dihydroxy-3-methyl-, and 5:6-dihydroxy-2:3-dimethyl-indole are described. In faintly alkaline solution the behaviour of these compounds differs from that of 5:6-dihydroxyindole (Part I, *J.*, 1948, 2223).

The results of preliminary experiments on the autoxidation of 5:6-dihydroxyindole with the objective of defining the nature of the polymerisation process are recorded.

BOTH 5:6-dihydroxyindole and its 2-carboxylic acid have been regarded by Raper (*J.*, 1938, 125) as melanin precursors in the tyrosinase-catalysed oxidation of tyrosine. We have recently shown (Part I, *J.*, 1948, 2223) that the properties of authentic 5:6-dihydroxyindole, prepared by an unambiguous synthetical route, are consistent with this view and it seems probable from the spectrophotometric investigations of Mason (*J. Biol. Chem.*, 1948, **172**, 83) that the immediate melanin precursor in the conversion of tyrosine into melanin is the dihydroxyindole and not the carboxylic acid. In continuation of our synthetical approach to the melanin problem, we

have now prepared 5 : 6-*dihydroxyindole*-2-*carboxylic acid* by a modification of the well-known general synthesis which proceeds through an *o*-nitrophenylpyruvic acid.



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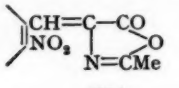

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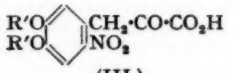

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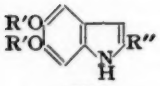

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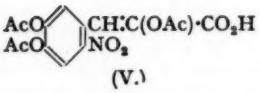

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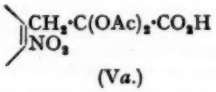


(V*a*.)

2-Nitroprotocatechualdehyde (I) was converted by way of a *monoacetate* of the azlactone (II) into 2-nitro-4 : 5-dihydroxyphenylpyruvic acid (III; R′ = H), which was characterised by formation of the *oxime*. Attempts to acetylate this pyruvic acid with acetic anhydride and sodium acetate resulted in the formation of intractable products but with a mixture of acetic anhydride and sulphuric acid at room temperature the required 2-*nitro*-4 : 5-*diacetoxyphenylpyruvic acid* (III; R′ = Ac) was obtained. When, however, the latter reaction was carried out at about 100° a different product was formed which, since it does not give the usual ferric reaction common to phenylpyruvic acids, may well be the triacetyl derivative (V) although the alternate possibility (V*a*) is not excluded.

Reductive cyclisation of the diacetate (III; R′ = Ac) to 5 : 6-*diacetoxyindole*-2-*carboxylic acid* (IV; R′ = Ac, R″ = CO_2H) was effected by treatment of the compound with iron powder and a mixture of acetic acid and ethanol, a modification of the normal procedure (first used by K. Clarke of this Department; unpublished work) which employs ferrous sulphate and aqueous ammonia. The reduction in acetic acid was preferred in order to avoid deacetylation of the initial compound and because of the marked sensitivity of the hydroxyindole derivatives already synthesised to alkaline reagents (Part I, *loc. cit.*). 5 : 6-Diacetoxyindole-2-carboxylic acid reacted normally with ethereal diazomethane to give the corresponding *methyl* ester.

Prepared by deacetylation of the diacetate by the sodium hydroxide–sodium hydrosulphite (dithionite) method employed in the synthesis of dihydroxyindole (Part I, *loc. cit.*), 5 : 6-dihydroxyindole-2-carboxylic acid (IV; R′ = H, R″ = CO_2H) proved to be a remarkably stable compound whose behaviour in faintly alkaline aqueous solution (*i.e.*, very dilute sodium hydrogen carbonate) is in striking contrast to that of 5 : 6-dihydroxyindole. With the acid, oxidation occurs only very slowly, giving in the course of 24 hours a dark brown solution but not an insoluble precipitate of the melanin type. Thus it seems unlikely that 5 : 6-dihydroxyindole-2-carboxylic acid is a melanin precursor, although it may be argued that in the presence of tyrosinase, oxidation to an insoluble melanin would occur. A study of the action of tyrosinase on this and other dihydroxyindoles will form the subject of a later paper in this series. In the meantime Professor C. E. H. Bawn and Mr. A. G. White of this University are engaged on a comprehensive quantitative study of the oxidative polymerisation of 5 : 6-dihydroxyindole. From their preliminary experiments they have reported the following observations :

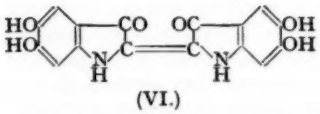
" Preliminary experiments on the autoxidation of 5 : 6-dihydroxyindole in phosphate buffer solution have been carried out with the primary object of establishing the stoicheiometry of the process, and also to obtain information on the kinetics in the hope that this would be of some assistance in the elucidation of the mechanism of the polymeric reaction involved.

" The uptake of oxygen was found to be of the type usually associated with oxidative chain reactions. Initially there was an induction period during which no uptake of oxygen was observable, but once oxygen uptake had commenced the rate of absorption rapidly became constant until a large part of the total had been absorbed when it decreased rapidly to zero. On dissolving the dihydroxyindole in the phosphate buffer solution used as solvent there was no apparent change for some minutes, after which a violet coloration developed, rapidly deepening until eventually a black precipitate was formed. It was noted that the appearance of the violet coloration coincided approximately with the end of the induction period in the oxygen uptake experiments.

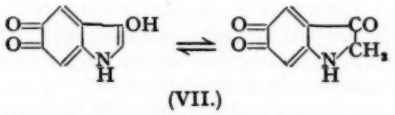
" From a study of the data so far obtained it is clear that the results are not readily reproducible and there is evidence of the reaction being susceptible to trace-metal catalysis."

In recent years a number of workers have speculated on the structure of melanin produced from 5 : 6-dihydroxyindole. Clemo and Weiss (*J.*, 1945, 702) have suggested, for example, that the oxidation involves the formation of tetrahydroxyindigotin (VI), but this now appears

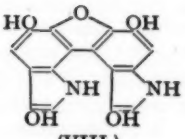
unlikely in view of the properties of the 5 : 6 : 5′ : 6′-tetrahydroxyindigotin prepared by Harley-Mason (*J.*, 1948, 1244). Cohen (*Bull. Soc. Chim. biol.*, 1946, **28**, 104, 107, 354) has indicated the possibility that the polymerising intermediate may be 3-hydroxyindole-5 : 6-quinone (VII), which would have a reactive methylene group and may therefore be capable of self-condensation. On the basis of analytical results obtained for melanins formed enzymically, Burton (*Chem. and Ind.*, 1947, 383) has proposed the empirical formula $C_{18}H_{10}O_5N_2$ for the melanin from tyrosine and in a later paper (*ibid.*, 1948, 313) this author has tried to account for his formula by postulating diphenylene oxide structures (*e.g.*, type VIII) as being possible intermediates, although it is admitted that further dehydrogenative coupling would lead to a polymer with a lower hydrogen content.



(VI.)



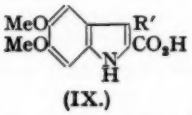
(VII.)



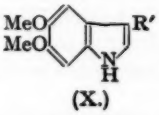
(VIII.)

The foregoing speculations involve the introduction of a hydroxyl-group into the β-position of the 5 : 6-dihydroxyindole nucleus, a process which is not altogether unlikely in view of the known tendency of indole itself to undergo oxidation in this position (compare Clemo and Weiss, *loc. cit.*). For this reason, it seemed to us a matter of some interest to study the properties and, in particular, the behaviour on oxidation of 5 : 6-dihydroxyindoles in which the β-position was already blocked by a substituent.

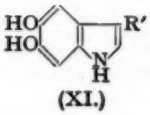
Since Hoshino and Shimodaira (*Bull. Chem. Soc. Japan*, 1936, **11**, 221) were able to demethylate bufotenin methyl ether (a β-substituted indole) with aluminium chloride, it appeared that this method might be applied to the preparation of the desired β-substituted 5 : 6-dihydroxyindoles, type (XI), from the corresponding dimethyl ethers (X).



(IX.)



(X.)



(XI.)

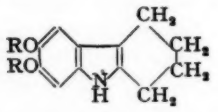
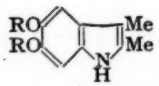
Both 5 : 6-*dimethoxy*-3-*phenyl*- (X; R′ = Ph) and 5 : 6-*dimethoxy*-3-*methyl-indole* (X; R′ = Me) were prepared by decarboxylation of the corresponding 2-carboxylic acids, which are readily available as a result of the work of Lions and Spruson (*J. Proc. Roy. Soc. N.S.W.*, 1932—1933, **66**, 171). The 3-phenylindole (X; R′ = Ph) was successfully demethylated by treatment with aluminium chloride in boiling benzene, giving 5 : 6-*dihydroxy*-3-*phenylindole* (XI; R′ = Ph) but when demethylation of the 3-methylindole (X; R′ = Me) was attempted, with either aluminium chloride or bromide under similar conditions, only traces of impure alkali-soluble products were isolated. It was subsequently found that 5 : 6-dimethoxy-3-methylindole-2-carboxylic acid (IX; R′ = Me) could be satisfactorily demethylated with aluminium bromide and on being heated in a high vacuum the resulting 5 : 6-dihydroxy-3-methylindole-2-carboxylic acid, which could not be satisfactorily purified, readily underwent decarboxylation yielding 5 : 6-*dihydroxy*-3-*methylindole* (XI; R′ = Me).

5 : 6-Dihydroxy-3-phenylindole proved to be so sparingly soluble in water that its sensitivity to aerial oxidation in faintly alkaline solution could not be satisfactorily determined. 5 : 6-Dihydroxy-3-methylindole, however, is more readily soluble, and when its aqueous solution is made faintly alkaline by addition of a trace of dilute sodium hydrogen carbonate solution rapid oxidation occurs, leading to the formation of a highly pigmented precipitate. This oxidation process, however, appears to differ from oxidations of 5 : 6-dihydroxyindole and 5 : 6-dihydroxy-2-methylindole (Part I, *loc. cit.*) carried out under comparative conditions in that the latter compounds give purple or brownish-red solutions in the early stages of the oxidation and later black precipitates, whereas the 3-methylindole gives a transient pure blue solution which soon deposits a blue precipitate. Whilst the precise significance of these differences is not clear at present, the results suggest that the oxidation of 5 : 6-dihydroxy-3-methylindole proceeds by a route which is different from that of 5 : 6-dihydroxyindole itself. This would be true if the latter oxidation involved attack at the 3-position of the indole nucleus.

The concept of studying the process of melanin formation by investigating the sensitivity of substituted dihydroxy-indoles towards oxidation is not a new one. Thus Clemo and Weiss

(*loc. cit.*) attempted the preparation of 5 : 6-dihydroxy-2 : 3-dimethylindole, by demethylenation of the related methylenedioxy-compound, in order to test their theory that the production of melanin was preceded by indigotin-formation.

We have studied the demethylation of 6 : 7-dimethoxy-1 : 2 : 3 : 4-tetrahydrocarbazole (XII; R = Me) and, subsequently, of 5 : 6-*dimethoxy*-2 : 3-*dimethylindole* (XIII; R = Me).

(XII.)   (XIII.)

In the former case, demethylation was accomplished in good yield with aluminium chloride in boiling benzene and the same product, 6 : 7-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (XII; R = H), was obtained by the action of aluminium bromide on 6 : 7-methylenedioxytetrahydrocarbazole. The dihydroxytetrahydrocarbazole oxidises only slowly in faintly alkaline aqueous solution, giving eventually a brown solution but not apparently an insoluble melanin-like product.

5 : 6-Dimethoxy-2 : 3-dimethylindole, obtained by an adaption of the Fischer method used by Clemo and Weiss (*loc. cit.*) for the preparation of the corresponding methylenedioxy-compound, was successfully demethylated with aluminium bromide in hot benzene. The resulting 5 : 6-*dihydroxy*-2 : 3-*dimethylindole* (XIII; R = H) oxidised more rapidly in alkaline media than the above dihydroxytetrahydrocarbazole but again a highly insoluble polymer was not formed.

In the course of this work it was observed that when the dimethoxytetrahydrocarbazole (XII; R = Me), prepared by the method of Lions *et al.* (*J. Proc. Roy. Soc. N.S.W.*, 1937—1938, **71**, 428), was recrystallised from light petroleum and subsequently from light petroleum–ethyl acetate, a change to a new compound of higher melting point and decreased solubility occurred. From the analytical results obtained the new compound was found to have the empirical formula $C_{14}H_{17}O_4N$, having been formed by the addition of a molecule of oxygen to the tetrahydrocarbazole, and, since it liberated iodine from an acidified aqueous solution of potassium iodide and decomposed vigorously when heated, this product is regarded as a *peroxide* or *hydroperoxide* of 6 : 7-dimethoxytetrahydrocarbazole. A more detailed account of the studies on this topic will be submitted when experiments now in progress have been completed.

Experimental.

2-*Nitro*-4 : 5-*dihydroxyphenylpyruvic Acid* (III; R′ = H).—An intimate mixture of 2-nitro-4 : 5-dihydroxybenzaldehyde (1·0 g., Part I, *loc. cit.*), aceturic acid (1·0 g.), acetic anhydride (3 ml.), and fused sodium acetate (1·0 g.)was heated on the steam-bath for ½ hour. Treatment of the cooled reaction mixture with water then afforded a slightly sticky solid which was triturated with a very small amount of ethyl alcohol, leaving a *monoacetate* of 4-(2′-nitro-4′ : 5′-dihydroxyphenyl)-2-methyloxazol-5-one as a granular yellow powder (m. p. 134—138°; 1·2 g.) sufficiently pure for use in the next stage of the synthesis. A pure sample was prepared by crystallisation from ethanol and formed elongated yellow needles, m. p. 140—142° (Found : N, 8·9, 9·1. $C_{13}H_{10}O_7N_2$ requires N, 9·15%). This compound was readily soluble in dilute aqueous sodium hydroxide, giving an intense purple solution.

The azlactone (1·0 g.) was heated on the steam-bath with 1% hydrochloric acid (60 ml.) for 4 hours and the resulting 2-nitro-4 : 5-dihydroxyphenylpyruvic acid was isolated from the cooled and filtered solution by means of ether, being obtained as a light yellow gum (0·6 g.) which slowly crystallised. This acid was characterised by the formation of the *oxime* which separated from acetic acid in hemispherical clusters of colourless needles, m. p. 178—179° (Found : N, 10·7. $C_9H_8O_7N_2$ requires N, 10·9%).

2-*Nitro*-4 : 5-*diacetoxyphenylpyruvic Acid* (III; R′ = Ac).—On the addition of a small drop of concentrated sulphuric acid to a solution of 2-nitro-4 : 5-dihydroxyphenylpyruvic acid (0·6 g.) in acetic anhydride (2 ml.), which had been prepared at about 50° and then cooled to room temperature, the mixture became warm and darkened. 10 Minutes later water (6 ml.) was introduced and the product triturated, with cooling, until it solidified. Collected after 24 hours, the *diacetyl* derivative (0·6 g.) was sufficiently pure for use in the next stage and on recrystallisation from the minimum quantity of hot 95% alcohol a sample was obtained in bright yellow prisms, m. p. 154—155°, giving a green ferric reaction in alcohol (Found : N, 4·2. $C_{13}H_{11}O_9N$ requires N, 4·3%).

When this acetylation was effected on the steam-bath for 10 minutes, a different product was obtained which is presumably the *triacetyl* derivative (V). This compound crystallised from alcohol in colourless prisms (0·6 g.), m. p. 152° (depressed by admixture with the foregoing diacetate), and did not give a coloration with ferric chloride in alcohol (Found : N, 3·8. $C_{15}H_{13}O_{10}N$ requires N, 3·8. $C_{17}H_{17}O_{12}N$ requires N, 3·5%).

5 : 6-*Diacetoxyindole*-2-*carboxylic Acid* (IV; R′ = Ac, R″ = CO_2H).—A solution of 2-nitro-4 : 5-diacetoxyphenylpyruvic acid (2·0 g.) in a mixture of acetic acid (40 ml.) and alcohol (50 ml.) was warmed with iron powder (10 g.) until a reaction set in which was then maintained by occasional heating over a period of 12 minutes. The mixture was then filtered, the solid residue was washed with several small portions of hot alcohol, and the combined filtrate and washings were diluted with water and extracted repeatedly with ether. The dark brown semi-solid obtained by evaporation of the combined dried

extracts was washed with a little cold methanol and then crystallised from the same solvent, giving 5 : 6-*diacetoxyindole-2-carboxylic acid* in buff squat prisms (0·83 g.), m. p. 256° (decomp.) (Found: C, 56·3; H, 3·9. $C_{13}H_{11}O_6N$ requires C, 56·3; H, 4·0%). It was sparingly soluble in ether and benzene but more soluble in alcohol, acetone, or chloroform, and gave a negative test with Ehrlich's reagent. Formed by the action of diazomethane on either a suspension of the acid in ether or a solution in dioxan, the *methyl ester* crystallised from alcohol in slender colourless needles, m. p. 179° (Found: C, 58·0; H, 4·4; N, 4·8. $C_{14}H_{13}O_6N$ requires C, 57·7; H, 4·5; N, 4·8%).

5 : 6-*Dihydroxyindole-2-carboxylic Acid* (IV; R′ = H, R″ = CO_2H).—Deacetylation of 5 : 6-diacetoxyindole-2-carboxylic acid (0·2 g.) was effected by application of the sodium hydroxide–sodium hydrosulphite (dithionite) method already described for the hydrolysis of 5 : 6-diacetoxyindole (Part I, *loc. cit.*), with the modification that a larger quantity of acetic acid (2 ml.) was used to acidify the alkaline reaction mixture. The crude *dihydroxy*-compound (70 mg.) was isolated with ether and purified from dilute acetic acid, forming almost white elongated prisms which on being heated darkened at about 225°, and then melted at 234° (decomp.) (Found: C, 55·3; H, 3·7; N, 7·1. $C_9H_7O_4N$ requires C, 55·9; H, 3·6; N, 7·2%). This acid is readily soluble in alcohol and in warm acetic acid, acetone, or water, but is sparingly soluble in hot ether, chloroform or carbon tetrachloride. In alcoholic solution, the compound gives an intense indigo-blue coloration with ferric chloride but does not give a coloration with Ehrlich's reagent. The addition of a drop of aqueous sodium hydroxide to an aqueous-alcoholic solution of the indolecarboxylic acid containing sodium nitroprusside produces an orange coloration, changing to greenish-blue on acidification with dilute acetic acid. In an aqueous solution made slightly alkaline by addition of a trace of sodium hydrogen carbonate, this dihydroxyindole derivative is very much more stable than 5 : 6-dihydroxyindole itself and does not appear to undergo the characteristic rapid oxidative polymerisation leading to melanin-like pigments.

An attempted purification of 5 : 6-dihyroxyindole-2-carboxylic acid by sublimation in a high vacuum afforded a colourless crystalline product, m. p. 140°, identified as 5 : 6-dihyrodroxyindole.

5 : 6-*Dimethoxy-3-phenylindole* (X; R′ = Ph).—5 : 6-Dimethoxy-3-phenylindole-2-carboxylic acid (Lions and Spruson, *J. Proc. Roy. Soc. N.S.W.*, 1932—1933, **66**, 171) (1·6 g.) was decarboxylated by being heated in a vacuum at 0·2 mm. Evolution of carbon dioxide commenced at a bath temperature of 150° and 5 : 6-*dimethoxy-3-phenylindole* sublimed as a hard glass which on crystallisation from ligroin afforded colourless feathery needles (1·0 g.), m. p. 137° (Found: C, 75·9; H, 5·8. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 5·9%). This compound, which darkens on prolonged exposure to air, gives a blue-green coloration, changing to blue, with Ehrlich's reagent at room temperature.

5 : 6-*Dihydroxy-3-phenylindole* (XI; R′ = Ph).—A solution of the foregoing dimethoxyindole (0·67 g.) in benzene (18 ml.) was heated under reflux with aluminium chloride (3·83 g.) for 10 hours, cooled in an ice-bath, and treated with ice-cold dilute hydrochloric acid followed by ether. The two layers were separated, the aqueous layer was extracted with further portions of ether, and the ether–benzene extracts were combined, dried, and concentrated by gentle warming in a stream of nitrogen until crystallisation commenced. The crude *dihydroxy*-compound (0·45 g.) was recrystallised from acetic acid, forming colourless plates, m. p. 256° (decomp.), which gave a strong violet coloration with Ehrlich's reagent, a purple ferric chloride reaction in alcohol, and a sticky red picrate in benzene solution (Found: C, 74·5; H, 5·1; N, 6·3. $C_{14}H_{11}O_2N$ requires: C, 74·7; H, 4·9; N, 6·2%).

5 : 6-*Dimethoxy-3-methylindole* (X; R′ = Me).—On being heated in a high vacuum 5 : 6-dimethoxy-3-methylindole-2-carboxylic acid (Lions and Spruson, *loc. cit.*) (1·6 g.) sublimed with only partial decomposition, and decarboxylation was best effected by subjecting the compound to distillation in a vacuum at 20 mm., thus affording 5 : 6-*dimethoxy-3-methylindole* (1·05 g.) which crystallised from ligroin in clusters of colourless needles, m. p. 150° (Found: C, 68·9; H, 7·0. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8%). With Ehrlich's reagent this indole gave a bluish-green coloration, changing to blue on being kept. Attempts to demethylate this compound by the aluminium bromide method gave only low yields of impure products.

5 : 6-*Dihydroxy-3-methylindole* (XI; R′ = Me).—A solution of 5 : 6-dimethoxyindole-2-carboxylic acid (1·6 g.) in benzene (125 ml.) was heated under reflux with aluminium bromide (9·1 g.) for 5 hours and the product isolated by the procedure described for the preparation of 5 : 6-dihydroxy-3-phenylindole. Thus prepared, 5 : 6-dihydroxy-3-methylindole-2-carboxylic acid (0·65 g.) separated as a grey solid, m. p. 158° (decomp.), which could not be recrystallised satisfactorily. Addition of benzene to an ether solution gave a greyish precipitate, m. p. 158° (decomp.) (Found: C, 57·1; H, 4·4. Calc. for $C_{10}H_9O_4N$: C, 58·0; H, 4·4%).

The foregoing acid (0·25 g.) was decarboxylated by being heated in a high vacuum [130—150° (bath)/0·001 mm.] and the resulting crystalline sublimate of 5 : 6-*dihydroxy-3-methylindole* dissolved in hot benzene–light petroleum. On cooling, the solution deposited the indole in colourless micaceous plates (0·16 g.), m. p. 152° (Found: C, 66·3; H, 5·3. $C_9H_9O_2N$ requires C, 66·3; H, 5·5%). This compound, which gives a bluish-violet Ehrlich reaction, a deep blue coloration with alcoholic ferric chloride, and a red crystalline picrate in benzene, is readily soluble in alcohol, ethyl acetate, acetic acid, or benzene, and moderately soluble in water. In very dilute aqueous sodium hydrogen carbonate, the 5 : 6-dihydroxy-3-methylindole oxidises rapidly, the solution acquiring a pure blue tint in a few minutes and subsequently depositing a blue precipitate which becomes darker on being kept further. This blue substance is insoluble in the usual organic solvents and in 2N-sodium hydroxide.

6 : 7-*Dimethoxy-1 : 2 : 3 : 4-tetrahydrocarbazole* (XII; R = Me) *and its Peroxide*.—The tetrahydrocarbazole was prepared from chloro*cyclo*hexanone and 4-aminoveratrole by the method of Lions *et al.* (*J. Proc. Roy. Soc. N.S.W.*, 1937, **71**, 428). The yellow glass obtained by the distillation of the crude product in a vacuum was triturated with a little alcohol and the resulting white solid recrystallised from dilute alcohol, giving the carbazole in long colourless needles, m. p. 105—106° (Found: C, 72·6; H, 7·6. Calc. for $C_{14}H_{17}O_2N$: C, 72·7; H, 7·4%) (Lions *et al.*, *loc. cit.*, record m. p. 98°). When the yellow glass was solidified by trituration with light petroleum, the colourless product had m. p. 99°. Successive recrystallisations of this material, first from light petroleum (b. p. 60—80°; an ordinary commerical sample was used) and, subsequently from ethyl acetate–light petroleum (b. p. 60—80°), brought about a rise in melting point and a marked decrease in solubility. The product, which was finally obtained in

almost colourless needles, m. p. 118° (with vigorous gas evolution), liberated iodine from an acidified aqueous solution of potassium iodide and is therefore regarded as a *peroxide* or, more probably, a *hydroperoxide* of the tetrahydrocarbazole (Found: C, 64·1, 64·0; H, 6·6, 6·3; N, 5·8, 6·0. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%).

6 : 7-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (XII; R = H).—A solution of 6 : 7-dimethoxytetrahydrocarbazole (1·0 g., m. p. 105°) in benzene (50 ml.) was heated with aluminium chloride (6·1 g.) for 11 hours and, on isolation by the procedure already described, the resulting 6 : 7-*dihydroxytetrahydrocarbazole* (0·8 g.) was crystallised from benzene (charcoal) in an atmosphere of nitrogen, forming almost white prisms, m. p. 175°. The same product (0·55 g.), m. p. and mixed m. p. 175°, was obtained when 6 : 7-methylenedioxy-1 : 2 : 3 : 4-tetrahydrocarbazole (1·0 g.) (Clemo and Weiss, *loc. cit.*) was heated in benzene with aluminium bromide (6·0 g.) for 4½ hours (Found: C, 70·9; H, 6·3; N, 6·9. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4; N, 6·9%). 6 : 7-Dihydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole is sparingly soluble in water and more soluble in ethanol, acetone, ether, and warm benzene. In alcoholic solution the compound gave a sepia coloration with ferric chloride whilst in very dilute aqueous sodium hydrogen carbonate it oxidised slowly giving a brown solution, but an insoluble melanin-like product was not formed even after prolonged storage.

(With J. S. E. Holker.)

5 : 6-*Dimethoxy*-2 : 3-*dimethylindole* (XIII; R′ = Me).—The method used was an adaptation of the procedure of Clemo and Weiss (*loc. cit.*) for the preparation of the corresponding methylenedioxy-compound. Sodium nitrite (2·8 g.) in water (28 ml.) was added in the course of 20 minutes to a mechanically stirred solution of 4-aminoveratrole (6·2 g.) in a mixture of concentrated hydrochloric acid (30 ml.) and water (32 ml.) maintained at −5°. The diazotised solution was then cooled to −15° and a solution of stannous chloride (22·4 g.) in concentrated hydrochloric acid (18 ml.) added during ½ hour, the temperature being allowed to rise to −10°. After having been kept at −10° for a further ½ hour, the resulting phenylhydrazine hydrochloride was collected and crystallised from alcohol, forming pale buff plates (5·5 g.), m. p. 164—165° (decomp.) (compare Perkin and Rubenstein, *J.*, 1926, 357, who give m. p. 162°).

A mixture of methyl ethyl ketone (3·0 ml.) and acetic acid (6 drops) was added to a solution of the foregoing phenylhydrazine hydrochloride (5·5 g.) and fused sodium acetate (2·4 g.) in absolute alcohol (70 ml.), and the mixture (protected from extraneous moisture) heated under reflux for 1½ hours. The filtered reaction mixture was cooled to 0°, saturated with dry hydrogen chloride, kept at 0° for ½ hour, and then heated under reflux for 1½ hours. Next day the solvent was evaporated under reduced pressure and the residue was washed with 2N-aqueous sodium hydroxide and then with water. From this material 5 : 6-*dimethoxy*-2 : 3-*dimethylindole* (1·80 g.) was isolated by repeated extraction with hot light petroleum (b. p. 80—100°) and recrystallised twice from aqueous acetone, forming long colourless prisms, m. p. 110·5° (Found: C, 70·1; H, 7·5. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·4%). This indole gave a red crystalline picrate but not an Ehrlich reaction.

5 : 6-*Dihydroxy*-2 : 3-*dimethylindole* (XIII; R = H).—A solution of 5 : 6-dimethoxy-2 : 3-dimethylindole (0·8 g.), in dry thiophen-free benzene (90 c.c.), was heated under reflux with powdered aluminium bromide (4·6 g.) for 4½ hours, cooled, treated with crushed ice and concentrated hydrochloric acid, and extracted with peroxide-free ether. The ether and most of the benzene were removed from the dried extract by evaporation in a stream of dry nitrogen and 5 : 6-*dihydroxy*-2 : 3-*dimethylindole*, which separated as an almost colourless solid (0·52 g.), was purified by sublimation at 150°/0·001 mm., being obtained in long colourless needles, m. p. *ca.* 189° (decomp.—preheated bath) (Found: C, 67·7; H, 6·4. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3%). The compound gave a brown coloration with alcoholic ferric chloride and oxidised fairly rapidly in dilute sodium hydrogen carbonate solution, giving a brownish-purple solution but a precipitate did not separate even after a long time.

University of Liverpool. [*Received, April 5th*, 1949.]

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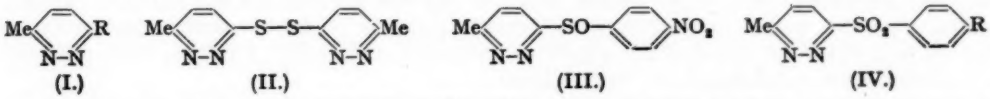
442. *The Conversion of Sucrose into Pyridazine Derivatives. Part VII. Some Sulphone Derivatives of 6-Methylpyridazine and 6-Methyl-3-pyridazone.*

By Hilda Gregory, W. G. Overend, and L. F. Wiggins.

The synthesis of *p*-aminophenyl 6-methyl-3-pyridazyl sulphone and some attempts to prepare *p*-aminophenyl 6-methylpyridaz-3-on-2-yl sulphone are described.

Sulphanilamide derivatives incorporating pyrimidine and pyrazine residues have been used with marked success in chemotherapy. Similar derivatives of pyridazine are less well known but one of them, 3-sulphanilamido-6-methylpyridazine (Overend and Wiggins, *J.*, 1947, 239; Roblin and Winnek, B.P. 563,629), shows promise of usefulness inasmuch as it displays a greater bacteriostatic activity than does sulphathiazole when examined under *in vitro* conditions. In recent years it has been shown that certain sulphones have powerful bacteriostatic activity. Thus, it has been shown that the 4 : 4′-diaminodiphenyl sulphone of Fromm and Wittman (*Ber.*, 1908, **41**, 2264) has a hundred times the curative effect of sulphanilamide on hæmolytic streptococcal infections in mice. Moreover, it has some chemotherapeutic efficacy in cases of

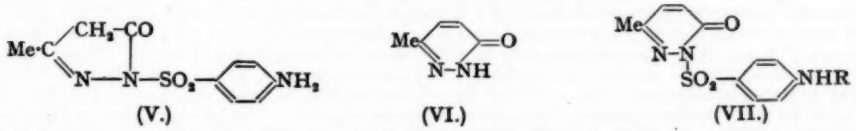
experimental tuberculosis (Feldman, Hinshaw, and Moses, *Amer. J. Med. Sci.*, 1944, **207**, 290), but its toxicity diminishes its clinical value. More recently, in attempts to find less toxic analogues the phenyl residues have been replaced by certain heterocyclic groups, and Bambas (*J. Amer. Chem. Soc.*, 1945, **67**, 668) has shown that the bacteriostatic activity is maintained so long as at least one phenyl group is left in the molecule—when both phenyl groups are replaced by heterocyclic residues, the activity vanishes. Moreover, Tullar and Banks (Abstracts of the St. Louis Meeting of the Amer. Chem. Soc., Division of Med. Chem., 1944, No. 5) demonstrated that for maintenance of activity it was necessary to include at least one amino-group situated *para* with respect to the sulphone group. It was also shown that only one amino-group was necessary to give an active substance. Thus, *p*-aminophenyl *p'*-hydroxyphenyl sulphone exhibited bacteriostatic activity. With these facts in our mind, the preparation of sulphone derivatives of pyridazine was attempted.



(I.) (II.) (III.) (IV.)

In Part V of this series (*J.*, 1948, 2199) methods were described for the preparation of 3-mercapto-6-methylpyridazine (I; R = SH) and for its conversion into 3-ethylthio-6-methylpyridazine (I; R = SEt). Now it has been found possible to oxidise this either with acid potassium permanganate at 0° or with 30% hydrogen peroxide at room temperature, to yield crystalline 6-*methyl*-3-*pyridazyl ethyl sulphone* (I; R = SO_2·Et). Attempts to prepare 3-phenylthio-6-methylpyridazine by heating 3-mercapto-6-methylpyridazine with iodobenzene at 150—160° were unsuccessful and instead *di*-(6-*methyl*-3-*pyridazyl*) *disulphide* (II) and unchanged starting material were isolated. This disulphide was also obtained when 3-mercapto-6-methylpyridazine was treated with aqueous ammonia, and the original thiol was regenerated by treatment with dilute sodium hydroxide solution followed by acidification. However, 3-mercapto-6-methylpyridazine condensed with *p*-bromonitrobenzene in the presence of alcoholic sodium methoxide at 80°, to give crystalline 3-p-*nitrophenylthio*-6-*methylpyridazine* (I; R = *p*-NO_2·C_6H_4·S·) in moderate yield. Oxidation of this with 30% hydrogen peroxide did not give the expected sulphone (IV; R = NO_2), but instead p-*nitrophenyl* 6-*methyl*-3-*pyridazyl sulphoxide* (III) was formed. The same compound was obtained when the theoretical amount of potassium permanganate was used as the oxidizing agent, although an excess of permanganate gave p-*nitrophenyl* 6-*methyl*-3-*pyridazyl sulphone* (IV; R = NO_2), which was also obtained when the sulphoxide itself was oxidized with potassium permanganate. Catalytic reduction of *p*-nitrophenyl 6-methyl-3-pyridazyl sulphone yielded p-*aminophenyl* 6-*methyl*-3-*pyridazyl sulphone* (IV; R = NH_2), isolated as the monohydrate. This sulphone exhibited no bacteriostatic activity *in vitro* against *Staphylococcus aureus*.

Few compounds of the sulphonamide class containing heterocyclic residues, described hitherto, possess a sulphanilyl residue attached to a nitrogen atom of the heterocyclic nucleus. One such compound is (V) prepared by Roblin *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 2002). The attempt has now been made to prepare a similar derivative of a pyridazone.



(V.) (VI.) (VII.)

It has been shown (Homer, Gregory, and Wiggins, *J.*, 1948, 2191) that alkylation of 6-methyl-3-pyridazone (VI) gives rise to 2-alkyl derivatives, and, when (VI) was treated with *N*-acetylsulphanilyl chloride, a compound was obtained which by analogy with the 2-alkyl derivatives of pyridazone is termed p-*acetamidophenyl* 6-*methylpyridaz*-3-*on*-2-*yl sulphone* (VII; R = Ac). Hydrolysis of this with sodium hydroxide or hydrochloric acid solution resulted in rupture of the nitrogen–sulphur linkage and regeneration of 6-methyl-3-pyridazone (VI). Consequently a more suitable residue with which to mask the amino-group in sulphanilyl chloride was sought, so that after the condensation the group protecting the amino-residue could be removed without use of either acid or alkaline reagents. The carbobenzyloxy-group appeared to answer these requirements since it can be removed from an amino-residue by catalytic hydrogenation under mild conditions.

Sodium N-*carbobenzyloxysulphanilate* was prepared by treating sodium sulphanilate in

aqueous solution with benzyl chloroformate and sodium hydrogen carbonate. Hydrogenation at room temperature in the presence of palladium resulted in cleavage of the carbobenzyloxy-residue and the formation of sodium sulphanilate. When dry sodium *N*-carbobenzyloxysulphanilate was intimately mixed with phosphorus pentachloride at room temperature it afforded crystalline N-*carbobenzyloxysulphanilyl chloride* which was converted into N-*carbobenzyloxysulphanilamide* on treatment with ammonia. Dohrn and Diedrich have previously (U.S.P. 2,411,495) prepared this compound by the condensation of sulphanilamide with benzyl chloroformate and record m. p. 192—192·5°. Whilst it was not possible to raise the m. p. of our compound above 189—190°, the similarity of these constants indicates that the compounds, although prepared in different ways, are identical. Hydrogenation of *N*-carbobenzyloxysulphanilamide was readily accomplished and sulphanilamide isolated. Treatment of 6-methyl-3-pyridazone (VI) with *N*-carbobenzyloxysulphanilyl chloride gave crystalline p-O-*benzylurethanophenyl* 6-*methylpyridaz*-3-*on*-2-*yl sulphone* (VII; R = $CH_2Ph{\cdot}O{\cdot}CO{\cdot}$). Hydrogenation of this in the conditions which were applied to *N*-carbobenzyloxysulphanilamide did not lead to the formation of the desired sulphone (VII; R = H); only sulphanilamide and *N*-carbobenzyloxysulphanilamide were isolated.

In bacteriostatic tests against *Staphylococcus aureus*, aqueous solutions of the acetyl derivative (VII; R = Ac) showed some inhibitory effect at a concentration of 1 : 500.

Experimental.

Di-(6-methyl-3-pyridazyl) Disulphide.—A solution of 3-mercapto-6-methylpyridazine (1 g.; *J.*, 1948, 2199) in a mixture of ethyl alcohol (50 c.c.) and 5N-aqueous ammonia (30 c.c.) was kept at room temperature for several days. The solution was then evaporated to dryness under reduced pressure, and the residue recrystallised from water, giving shining flakes of *di-(6-methyl-3-pyridazyl) disulphide*, (0·6 g.), m. p. 148° (Found: C, 47·9; H, 4·05; N, 22·4. $C_{10}H_{10}N_4S_2$ requires C, 48·0; H, 4·0; N, 22·4%). The compound was warmed in dilute sodium hydroxide solution, cooled, and acidified; 3-mercapto-6-methylpyridazine separated which, recrystallised from ethyl alcohol, had m. p. 203—205°.

Oxidation of 3-Ethylthio-6-methylpyridazine.—(*a*) To 3-ethylthio-6-methylpyridazine (0·77 g.; *J.*, 1948, 2199), dissolved in chloroform (10 c.c.), were added ice and 5N-sulphuric acid (10 c.c.). The mixture was cooled to 0° and potassium permanganate (0·63 g.) added slowly in portions. When the addition was complete, the mixture was allowed to reach room temperature, made alkaline, decolorised with sulphur dioxide, and extracted with chloroform. The dried ($MgSO_4$) chloroform extract was evaporated to dryness, and the residue recrystallised several times from benzene–light petroleum (b. p. 40—60°), giving 6-*methyl-3-pyridazyl ethyl sulphone* (0·35 g.), m. p. 107—108° (Found: C, 45·4; H, 5·5. $C_7H_{10}O_2N_2S$ requires C, 45·2; H, 5·4%).

(*b*) A solution of 3-ethylthio-6-methylpyridazine (0·77 g.) in acetic acid (5 c.c.) and hydrogen peroxide (30%; 5 g.) was set aside at room temperature for 3 days. The solution was diluted with water, neutralised (sodium hydroxide), and extracted with chloroform. The chloroform extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The syrupy residue crystallised on trituration with ether and, recrystallised from benzene–light petroleum (b. p. 40—60°), gave the sulphone (0·3 g.), m. p. 107—108°, alone or in admixture with the compound obtained as above.

Attempted Condensation of 3-Mercapto-6-methylpyridazine with Iodobenzene.—3-Mercapto-6-methylpyridazine (1·0 g.), iodobenzene (1·62 g.), and sodium hydroxide (0·32 g.) in ethyl alcohol (12 c.c.) were heated at 150—160° for 5 hours. The reaction mixture was evaporated to dryness under reduced pressure, and the unchanged iodobenzene was extracted with ether. The residue, recrystallised from water, afforded di-(6-methyl-3-pyridazyl) disulphide (0·3 g.), m. p. 148°, alone or in admixture with that previously prepared. The aqueous mother-liquors were acidified (hydrochloric acid), whereupon yellow needles of 3-mercapto-6-methylpyridazine (0·5 g.), m. p. 200—202°, were obtained.

3-p-*Nitrophenylthio-6-methylpyridazine.*—To 3-mercapto-6-methylpyridazine (3·25 g.) dissolved in dry ethyl alcohol was added a dry ethanolic solution of sodium methoxide (1·47 g.), followed by *p*-bromonitrobenzene (5·0 g.), and the mixture was heated on a water-bath for 5 hours. The concentrated solution deposited crystals (4·2 g.) on cooling. The mother-liquors were evaporated to dryness, the unchanged *p*-bromonitrobenzene was removed by steam-distillation, and the residue and the first crop of crystals were recrystallised several times from aqueous alcohol. The product, 3-p-*nitrophenylthio-6-methylpyridazine* (6·25 g.) had m. p. 142° (Found: C, 53·3; H, 3·80; N, 16·8. $C_{11}H_9O_2N_3S$ requires C, 53·4; H, 3·64; N, 17·0%).

Oxidation of 3-p-*Nitrophenylthio-6-methylpyridazine.*—(a) *By hydrogen peroxide.* 3-*p*-Nitrophenylthio-6-methylpyridazine (1·24 g.) was dissolved in acetic acid, and hydrogen peroxide (2·5 g.; 30%) was added. The solution was kept at room temperature for three days and then diluted with water, and sodium hydroxide solution was added until faint alkalinity was obtained. A yellow solid (1·2 g.) which separated was collected and after repeated crystallisation from 90% ethyl alcohol had m. p. 121—123°. It was p-*nitrophenyl 6-methyl-3-pyridazyl sulphoxide* (Found: C, 50·3; H, 3·53; N, 15·5. $C_{11}H_9O_3N_3S$ requires C, 50·2; H, 3·4; N, 16·0%).

(b) *By potassium permanganate.* (i) 3-*p*-Nitrophenylthio-6-methylpyridazine (1·24 g.) was dissolved in glacial acetic acid (25 c.c.), and a 5% solution of potassium permanganate (0·63 g.) was added slowly with shaking. Immediate oxidation occurred. When the addition was complete, the reaction mixture was heated to boiling, cooled, decolorised with sodium hydrogen sulphite, and extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and evaporated to dryness. The residue, recrystallised five times from 90% ethyl alcohol, gave *p*-nitrophenyl 6-methyl-3-pyridazyl sulphoxide (0·7 g.), m. p. 121—123°. (ii) The above experiment was repeated with 3-*p*-nitrophenylthio-6-methylpyridazine

(1·38 g.) and potassium permanganate (1·83 g.). On decolorisation with sodium hydrogen sulphite, pale yellow crystals of p-*nitrophenyl 6-methyl-3-pyridazyl sulphone* separated which, recrystallised from ethyl alcohol, formed nearly colourless needles (0·32 g.), m. p. 175°. Extraction of the mother-liquors with chloroform gave a further quantity (0·07 g.), m. p. 175° (Found: C, 47·7; H, 3·3; N, 14·7. $C_{11}H_9O_4N_3S$ requires C, 47·3; H, 3·2; N, 15·0%). Oxidation of *p*-nitrophenyl 6-methyl-3-pyridazyl sulphoxide with potassium permanganate in glacial acetic acid by the method described above also gave the sulphone, m. p. 175°, in 52% yield.

Reduction of p-*Nitrophenyl 6-Methyl-3-pyridazyl Sulphone.*—*p*-Nitrophenyl 6-methyl-3-pyridazyl sulphone (0·42 g.), suspended in ethyl alcohol (40 c.c.), was hydrogenated at room temperature with use of palladium on activated charcoal as a catalyst. Absorption of hydrogen ceased when the theoretical amount of hydrogen necessary for reduction to an amino-group had been absorbed. The mixture was filtered, and the solution evaporated to a syrup which, on trituration with alcohol, rapidly crystallised. p-*Aminophenyl 6-methyl-3-pyridazyl sulphone monohydrate* crystallised from water in fine colourless needles (0·28 g.), m. p. 120—121° (Found: C, 49·5; H, 4·9; N, 15·7. $C_{11}H_{11}O_2N_3S,H_2O$ requires C, 49·5; N, 4·8; N, 15·7%). Attempts to remove the water of crystallisation at 65° *in vacuo* were unsuccessful, and the use of higher temperatures resulted in decomposition of the compound.

p-*Acetamidophenyl 6-Methylpyridaz-3-on-2-yl Sulphone.*—Anhydrous 6-methyl-3-pyridazone (1 mol., 1·06 g.) was dissolved in dry pyridine (10 c.c.), and a solution of *N*-acetylsulphanilyl chloride (1·1 mol., 2·12 g.) in pyridine (10 c.c.) was added. The mixture was warmed to 45° for 1 hour and then poured into water (50 c.c.) containing sodium hydroxide (1 mol.; 0·39 g.). Concentration of the solution and removal of the pyridine afforded an oil which slowly crystallised. p-*Acetamidophenyl 3-methylpyridaz-6-on-1-yl sulphone monohydrate* crystallised from ethyl alcohol–water in shining white needles which gradually became pink when kept; m. p. 96—97°; yield, 1·16 g. (Found: C, 48·3; H, 5·1; N, 13·3. $C_{13}H_{13}O_4N_3S,H_2O$ requires C, 48·0; H, 4·6; N, 12·9%). Attempts to deacetylate this substance by warming it with dilute sodium hydroxide or with hydrochloric acid resulted in hydrolysis and the recovery of 6-methyl-3-pyridazone.

Sodium N-*Carbobenzyloxysulphanilate.*—To a solution of sodium sulphanilate (1·40 g.) in water (20 c.c.), sodium hydrogen carbonate (2 mols., 1·25 g.) and benzyl chloroformate (1 mol., 1·26 g.) were added. The mixture was shaken, whereupon a solid *sodium* salt separated. This was collected and recrystallised from alcohol–water from which it formed shining white triangular plates (48%), m. p. 250° (with darkening) (Found: C, 49·7; H, 3·7; N, 4·1. $C_{14}H_{12}O_5NSNa,\frac{1}{2}H_2O$ requires C, 49·7; H, 3·8; N, 4·1%). The compound (0·40 g.) in aqueous solution (20·0 c.c.) was hydrogenated at room temperature in the presence of palladium on activated charcoal. Slow absorption of hydrogen occurred and at the end of the reaction toluene was detected in the solution. The filtered solution was evaporated to dryness. The residue was recrystallised from water and identified as sodium sulphanilate (m. p. >200°) by conversion into sulphanilic acid (m. p. >300°).

N-*Carbobenzyloxysulphanilyl Chloride.*—Dry sodium *N*-carbobenzyloxysulphanilate (7·0 g.) and phosphorus pentachloride (7 g.) were ground together until a semi-liquid mass was obtained. The mixture was set aside *in vacuo* at room temperature for 4 hours and then mixed with ice. The solid which separated was collected and dried *in vacuo* over phosphoric oxide. The dry solid was extracted with boiling benzene, and the cooled, filtered extract evaporated. The residue, N-*carbobenzyloxysulphanilyl chloride*, crystallised from benzene in colourless needles (1·70 g.; 26·4%), m. p. 109—110° (Found: C, 52·0; H, 3·9; S, 9·2. $C_{14}H_{12}O_4NClS$ requires C, 51·7; H, 3·7; S, 9·8%).

N-*Carbobenzyloxysulphanilamide.*—*N*-Carbobenzyloxysulphanilyl chloride (0·2 g.) was suspended in dilute aqueous ammonia (5 c.c.), the suspension saturated 0° with gaseous ammonia, and the mixture kept at 0° for 10 days. The solid *N*-carbobenzyloxysulphanilamide (0·15 g.) was collected and had m. p. 169—172°. After this product had been crystallised six times from methyl alcohol, the m. p. was raised to 189—190°, the last three crystallisations not having affected the m. p. (Found: C, 54·3; H, 4·5. Calc. for $C_{14}H_{14}O_4N_2S$: C, 54·9; H, 4·6%).

Hydrogenation of N-*Carbobenzyloxysulphanilamide.*—*N*-Carbobenzyloxysulphanilamide (0·15 g.), suspended in water (5 c.c.), was hydrogenated at room temperature in the presence of palladium–charcoal. Slow absorption of hydrogen occurred. At the end of the reaction the solution was warmed and then filtered. Concentration of the filtrate yielded a solid, which, recrystallised from alcohol–water, formed colourless needles, m. p. 163° alone or in admixture with sulphanilamide.

p-O-*Benzylurethanophenyl 6-Methylpyridaz-3-on-2-yl Sulphone.*—A solution of *N*-carbobenzyloxysulphanilyl chloride (1·1 mol., 1·43 g.) in anhydrous pyridine (10 c.c.) was added to anhydrous 6-methyl-3-pyridazone (0·44 g.) in pyridine (5 c.c.). The mixture was set aside at room temperature overnight and was then poured into water. An oil separated which crystallised when kept. p-O-*Benzylurethanophenyl 6-methylpyridaz-3-on-2-yl sulphone* crystallised from alcohol–water in colourless needles, m. p. 146—147°; yield, 1·0 g. (57%) (Found: C, 56·9; H, 4·4; N, 10·6. $C_{19}H_{17}O_5N_3S$ requires C, 57·1; H, 4·2; N, 10·5%).

Hydrogenation of p-O-*Benzylurethanophenyl 6-Methylpyridaz-3-on-2-yl Sulphone.*—The sulphone (0·6 g.) in alcohol–water (50 c.c.) was hydrogenated at room temperature over palladium–charcoal. From the filtered concentrated solution a brown oil (0·20 g.) separated, but this could not be induced to crystallise and was not identified. The aqueous solution remaining was evaporated to a syrup which partly crystallised on nucleation with *N*-carbobenzyloxysulphanilamide. These crystals were collected and washed with water, and then had m. p. 168—171°, alone or in admixture with *N*-carbobenzyloxysulphanilamide (yield, 0·02 g.). The remainder of the syrup crystallised overnight and after recrystallisation from ethyl alcohol was shown to be identical with sulphanilamide, m. p. 163° (yield, 0·13 g.).

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443. *The Instability of Some Aminobenzyl Quaternary Salts.*

By C. G. Raison.

Of the *m*- and *p*-aminobenzyl quaternary salts of quinoline, *iso*quinoline, pyridine, and dimethylaniline, only the *m*-compounds are stable; the *p*-compounds decompose readily with liberation of the tertiary base and are stable only in the presence of mineral acid or as their acetyl derivatives. A mechanism for this abnormal instability is suggested, and its implications are discussed.

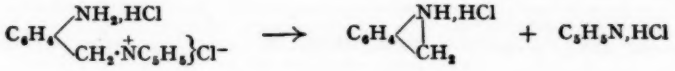
During a search for new trypanocidal drugs the aminobenzyl quaternary salts of a number of *N*-heterocyclic compounds were examined. Although failing to disclose any substance of biological interest, the work provided examples of abnormal instability in such salts.

The aminobenzylquinolinium salts were investigated in most detail. *p*-Nitrobenzylquinolinium chloride was prepared by von Walther and Weinhagen (*J. pr. Chem.*, 1917, **96**, 50), and in the experimental section is described an improved method of carrying out this type of condensation. Reduction of the nitro-group by means of Raney nickel in methanol, iron powder and water, or ferrous hydroxide gave quinoline in good yield as the only recognisable product. Removal of a benzyl residue by reduction is well known, and Snyder and Speck (*J. Amer. Chem. Soc.*, 1939, **61**, 668, 2895) have shown that in quaternary salts containing benzyl, that radical is removed by certain inorganic sulphur compounds. In the present example, however, it was considered unlikely that such a mild reducing agent as ferrous hydroxide would cause reductive debenzylation and, moreover, no trace of *p*-toluidine was detectable in the products of reduction by any of the above reagents.

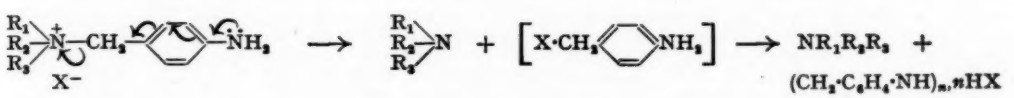
The situation was clarified when *p*-nitrobenzylquinolinium chloride was reduced at room temperature in dilute hydrochloric acid solution with hydrogen and palladised charcoal. Six atoms of hydrogen were smoothly absorbed and examination of the colourless filtrate established the following facts: (*a*) evaporation in a vacuum at low temperature left p-*aminobenzylquinolinium chloride hydrochloride* as a light-coloured, hygroscopic powder, fairly stable if stored in a dry state (*e.g.*, only slight decomposition after 3 weeks); (*b*) diazotisation and coupling under acid conditions with β-naphthylamine gave the expected red *azo*-compound; (*c*) on addition of sodium acetate the solution became orange and rapidly deposited orange-yellow needles of p-*aminobenzylquinolinium chloride* as a dihydrate, which could be dried rapidly in a vacuum and analysed, but very quickly began to smell of quinoline and after 3 weeks had undergone extensive decomposition; an aqueous solution of the crystals decomposed rapidly on being heated, giving a good yield of quinoline together with a brown amorphous substance; (*d*) addition of sodium acetate, followed by acetic anhydride, gave colourless p-*acetamidobenzylquinolinium chloride*, stable to boiling water.

o-*Aminobenzylquinolinium chloride* was similarly unstable but the m-*isomer* was found to be quite stable in hot aqueous solution. To investigate the generality of these observations, the *m*- and *p*-aminobenzyl quaternary *salts* of 6-amino- and 6-carbethoxyamino-quinoline, *iso*quinoline, pyridine, and dimethylaniline were prepared, in each case by reduction of the corresponding nitro-compound. Palladised charcoal and hydrogen smoothly and exclusively reduced the nitro-group, except for the two derivatives of dimethylaniline where this reagent, as well as Raney nickel and hydrogen, brought about further reduction at the quaternary centre with formation of the corresponding toluidines. The use of ferrous hydroxide, however, obviated this difficulty. In every example, the distinction between the *m*- and the *p*-isomer was clear-cut; the former was stable in hot aqueous solution, but the latter was rapidly broken down with liberation of the corresponding tertiary base and was stable only in the presence of excess of mineral acid or in the form of its acetyl derivative.

The instability of *p*-aminobenzylpyridinium chloride appears to have been recognised by the chemists of Meister, Lucius and Brüning (cf. D.R.-P. 123,613, 128,726) and also by Lellmann and Pekrun (*Annalen*, 1890, **259**, 40). The latter prepared all three isomeric aminobenzylpyridinium chloride hydrochlorides, but only for the *p*-isomer did they record their attempt to obtain the free amino-compound, noting the ease with which it broke down into pyridine and an amorphous substance. They were more interested in the decomposition which all the isomeric hydrochlorides underwent at temperatures above 200° and which they formulated thus:



Volatilisation of pyridine hydrochloride left a residue identified as the hydrochloride of the isomeric, amorphous (and probably polymeric) benzyleneimides. Formation of such a polymeric imide probably accounts for the amorphous substances which accompany the tertiary bases in the above decompositions of *o*- and *p*-aminobenzyl quaternary salts. The breakdown has been represented (preliminary communication; *Nature*, 1949, **163**, 485) in the manner shown below for a *p*-aminobenzyl salt, the strain in the benzyl–N bond due to the presence of



the adjacent positive charge being magnified to the point of rupture by the powerful electromeric effect of a *free* amino-group in the *p*-position. The greater stability of the *m*-isomers as well as that of the salts and acetyl derivatives of the *p*-isomers is then understandable. Apart from the German work on the pyridinium salts, however, the present observations, and the interpretation offered for them, appear to be new. Reilly and Drumm (*J.*, 1935, 871; see also Pressmann *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 250) have prepared trimethyl-*p*-aminobenzylammonium chloride hydrochloride, and all three isomeric 3-(aminobenzyl)-4-methylthiazolium chloride hydrochlorides have been described by Clark (*ibid.*, 1944, **66**, 652) and Livermore and Sealock (*J. Biol. Chem.*, 1947, **167**, 699), but in no instance was the free amino-quaternary salt examined.

The question arises whether groups other than amino- could cause similar instability in benzyl quaternary salts. It would appear that only those groups able to show a powerful electromeric effect (OH, OAlkyl) need be considered. Alkoxyl has a less pronounced effect than acetoamido (cf. influence on nitration in benzene derivatives, Ingold and Ingold, *J.*, 1926, 1310), and the literature reveals many instances of apparently stable *p*-alkoxybenzyl quaternary salts (quaternary salt formation is often reversed at higher temperatures but in the present discussion, " stability " is used in a restricted sense, applying to the temperature range 20—100°, particularly in aqueous solution). With hydroxybenzyl quaternary salts, examples are few and the position is not clear. Zemplén and Kunz (*Ber.*, 1922, **55**, 979) and Stedman (*J.*, 1927, 1902) have described trimethyl-*o*-hydroxybenzylammonium salts. On the other hand, Stedman and Stedman (*J.*, 1929, 609) studied the quaternisation of the three isomeric dimethylhydroxy-α-methylbenzylamines with methyl iodide and only in the case of the *m*-compound could they isolate a quaternary salt. The methiodides of the *o*- and *p*-compounds were unstable and, in the former case, elimination of the basic group was shown by the isolation of tetramethylammonium iodide. Of course, the presence of the α-methyl substituent would enhance the tendency to instability by the suggested mechanism.

If the above mechanism for these degradations is correct, the phenyl ring of the benzyl group acts solely as an electrical conductor of effects arising primarily in the substituent and suggests that instability might be found in quaternary salts carrying either amino- or hydroxymethyl groups. On both these points information is available. Whereas 2-aminoethyl quaternary salts have been prepared by acid hydrolysis of 2-phthalimidoethyl salts (*e.g.*, Gabriel, *Ber.*, 1920, **53**, 1985; Seshadri, *J.*, 1929, 2952), even excess of acid does not stabilise aminomethyl salts, for Kipping and Mann (*J.*, 1927, 528) found that phthalimidomethylpyridinium bromide, with hot dilute hydrochloric acid, gave phthalic acid, ammonia, formaldehyde, and pyridine. Many analogues of choline chloride (2-hydroxyethyl quaternary salts) have been described, but Stewart and Kung (*J. Amer. Chem. Soc.*, 1933, **55**, 4813) have shown that hydroxytetramethylammonium chloride (formocholine chloride) and hydroxymethyltriethylammonium chloride are decomposed very rapidly in solution in water, liberating the tertiary base and formaldehyde. Krŏhnke's observation (*Ber.*, 1933, **66**, 1386) that ω-bromophenacylpyridinium bromide is decomposed by hot water giving, *via* the corresponding hydroxy-compound, phenylglyoxal and pyridine is possibly another example of the same type of instability.

Steric Factors in the Formation of Nitrobenzyl Quaternary Salts.—Von Walther and Weinhagen (*loc. cit.*) observed that *p*-nitrobenzyl chloride condensed with pyridine, α-picoline, and quinoline but not with collidine or quinaldine. During the present work it has been found that reaction does not occur with 2- or 8-methyl- or 8-chloro-quinoline; it occurs with 8-methoxyquinoline, though more sluggishly than with quinoline, which itself reacts much less rapidly than pyridine or *iso*quinoline.

Experimental.

p-*Nitrobenzylquinolinium Salts.*—Von Walther and Weinhagen (*loc. cit.*) condensed quinoline with nitrobenzyl chlorides by heating the reactants together on the water-bath; after separation from a red pigment the products were characterised as dichromates. The yields are considerably improved and the formation of red pigment avoided if the condensation is carried out in boiling aqueous suspension. This method of preparing quaternary salts has proved very satisfactory throughout this work.

Quinoline (24 ml.), *p*-nitrobenzyl chloride (34·3 g.), water (200 ml.), and alcohol (50 ml.) were heated under reflux with stirring for 8 hours. After steam-distillation, the aqueous liquid was decanted from a little tar, decolorised with charcoal, and evaporated to dryness in a vacuum. Digestion of the residue with ethyl acetate and filtration gave p-*nitrobenzylquinolinium chloride* (80%), m. p. *ca.* 190°. Crystallisation from alcohol–ethyl acetate gave rosettes of colourless needles, m. p. 203—205° (Found: C, 63·5; H, 3·8; N, 9·35; Cl, 11·8. $C_{16}H_{13}O_2N_2Cl$ requires C, 63·9; H, 4·3; N, 9·3; Cl, 11·8%). The *iodide* formed stout yellow prisms from methyl alcohol, m. p. 186° (Found: C, 49·1; H, 3·6; N, 7·0; I, 32·6. $C_{16}H_{13}O_2N_2I$ requires C, 49·0; H, 3·3; N, 7·1; I, 32·4%).

p-*Aminobenzylquinolinium Salts and Derivatives.*—When the above nitro-compound (1 mole), in aqueous solution containing hydrochloric acid (2 moles), was shaken with hydrogen and palladised charcoal, 6 atoms of hydrogen were rapidly absorbed. The colourless filtrate was divided and used for the following experiments.

(*a*) Evaporation at low temperature in a vacuum and digestion of the residue with acetone left p-*aminobenzylquinolinium chloride hydrochloride* as a buff-coloured hygroscopic powder which softened at >80° and decomposed at 170—175°. Before analysis it was dried at 40° in a vacuum (Found: N, 9·1; Cl, 22·5. $C_{16}H_{16}N_2Cl_2$ requires N, 9·1; Cl, 23·1%).

(*b*) Diazotisation and coupling with β-naphthylamine in excess of hydrochloric acid gave an insoluble red *azo*-compound, deep red rosettes of prisms from alcohol; m. p. 154° (Found: N, 13·1; Cl, 8·0. $C_{26}H_{21}N_4Cl$ requires N, 13·2; Cl, 8·35%).

(*c*) On addition of sodium acetate the liquid became orange and then deposited orange-yellow needles of p-*aminobenzylquinolinium chloride*, which were washed with ice-water and rapidly dried in a high vacuum for immediate analysis (m. p. 87—88°) (Found: N, 8·9, 9·3; Cl, 11·4, 11·7. $C_{16}H_{15}N_2Cl,2H_2O$ requires N, 9·15; Cl, 11·6%). Warm solvents caused rapid decomposition. When the filtrate from the reduction was treated with sodium acetate and steam-distilled, quinoline was removed (picrate; 85% yield), leaving a brown amorphous powder, m. p. 179—184°, insoluble in boiling alcohol. Analysis suggested that this was the *acetate* of polymeric benzyleneimide [Found: N, 8·3, 8·45; Cl, nil. $(C_7H_7N)_n,nC_2H_4O_2$ requires N, 8·5%]; digestion with dilute sodium hydroxide left a similar amorphous powder, m. p. 180—190° [Found: N, 13·5, 13·7. $(C_7H_7N)_n$ requires N, 13·3%], presumably the free *imide*.

(*d*) Addition of sodium acetate was followed by the addition of acetic anhydride at <20° with stirring. A clear solution was formed, which then deposited colourless crystals (probably hydrated; m. p. 151—153°); crystallisation from alcohol gave p-*acetamidobenzylquinolinium chloride* as colourless woolly needles, m. p. 225° (Found: N, 8·9, 8·8; Cl, 11·1, 11·0. $C_{18}H_{17}ON_2Cl$ requires N, 8·95; Cl, 11·35%).* The *iodide* formed bright yellow prisms from alcohol; m. p. 207—208° (Found: C, 53·5; H, 4·65; N, 7·0; I, 31·3. $C_{18}H_{17}ON_2I$ requires C, 53·5; H, 4·2; N, 6·9; I, 31·4%).

o-*Nitrobenzylquinolinium Iodide.*—Quinoline and *o*-nitrobenzyl chloride (free from the *p*-isomer, having been synthesised from *o*-nitrotoluene) were condensed together, and the product was converted into the *iodide*, long golden-yellow needles, m. p. 203—204°, from methyl alcohol (Found: N, 7·0; I, 32·4. $C_{16}H_{13}O_2N_2I$ requires N, 7·1; I, 32·4%). This was converted into the chloride by means of silver chloride, and reduced in dilute hydrochloric acid with palladised charcoal and hydrogen; the filtrate, on treatment with sodium acetate followed by steam-distillation, gave a copious yield of quinoline (identified as picrate).

m-*Nitrobenzylquinolinium chloride*, prepared by the general method (66% yield), formed colourless prisms from alcohol–ethyl acetate; m. p. 196—197° (Found: N, 9·4; Cl, 11·6. $C_{16}H_{13}O_2N_2Cl$ requires N, 9·3; Cl, 11·8%).*

m-*Aminobenzylquinolinium Chloride.*—The above nitro-compound was reduced in dilute hydrochloric acid with palladised charcoal and hydrogen, and the filtrate evaporated to dryness in a vacuum. Crystallisation of the residue from 90% alcohol gave the *hydrochloride* in pale brown prisms, m. p. 231—233° (decomp.) (Found: C, 63·3; H, 5·8; N, 9·3; Cl, 22·8. $C_{16}H_{16}N_2Cl_2$ requires C, 62·6; H, 5·2; N, 9·1; Cl, 23·1%). The aqueous solution became yellow on addition of sodium acetate and could then be boiled without decomposition; addition of potassium iodide precipitated m-*aminobenzylquinolinium iodide*, dichromate-coloured prisms from methyl alcohol; m. p. 181—182° (Found: C, 53·6; H, 4·7; N, 7·6; I, 35·1. $C_{16}H_{15}N_2I$ requires C, 53·05; H, 4·15; N, 7·75; I, 35·1%).

6-*Amino*-p-*nitrobenzylquinolinium Chloride.*—6-Acetamidoquinoline (35·35 g.), *p*-nitrobenzyl chloride (32·6 g.), water (200 ml.), and alcohol (50 ml.) were stirred under reflux for 10 hours. The liquid was steam-distilled, treated with charcoal, heated for 2 hours on the steam-bath with half its volume of concentrated hydrochloric acid, and then evaporated to dryness. The residue was taken up in a little hot water, and the solution strongly cooled until the separated oil had become largely crystalline. The product was filtered off and digested with acetone, which left the required *chloride* as an orange crystalline powder, m. p. 182—183° (60% yield). This crystallised from 90% alcohol in orange leaflets of the same m. p. (Found: C, 60·6; H, 4·6; N, 13·2; Cl, 11·1. $C_{16}H_{14}O_2N_3Cl$ requires C, 60·8; H, 4·4; N, 13·3; Cl, 11·25%). The *iodide* formed orange prisms from 60% acetic acid; m. p. 221—222° (Found: N, 10·5; I, 31·4. $C_{16}H_{14}O_2N_3I$ requires N, 10·3; I, 31·2%).

The corresponding *p*-aminobenzyl salt, formed by reduction, was unstable.

6-*Amino*-m-*nitrobenzylquinolinium chloride*, prepared in the same manner as the *p*-isomer (50% yield), had m. p. 219° after crystallisation from 95% alcohol (Found: N, 13·4; Cl, 10·65%).

* Compounds marked thus did not give reproducible values for C and H.

6-*Amino*-m-*aminobenzylquinolinium chloride* separated after catalytic reduction of the above nitro-compound and addition of sodium acetate; it crystallised from hot water in long orange needles, m. p. indefinite >125° (Found: N, 14·55; Cl, 12·5. $C_{16}H_{16}N_3Cl$ requires N, 14·7; Cl, 12·4%).

6-*Carbethoxyaminoquinoline*.—6-Aminoquinoline (28·8 g.), alcohol (100 ml.), and diethylaniline (35 ml.) were heated on a steam-bath, and ethyl chloroformate (20 ml.) was added gradually; after a further ½ hour's boiling, the mixture was poured into water, and the *product* (40 g.) collected and dried. It separated from methyl alcohol as colourless tablets, m. p. 168—168·5° (Found: N, 13·3. $C_{12}H_{12}O_2N_2$ requires N, 13·0%).

6-*Carbethoxyamino*-p-*nitrobenzylquinolinium Chloride*.—6-Carbethoxyaminoquinoline (20 g.), *p*-nitrobenzyl chloride (15·9 g.), water (100 ml.), and alcohol (25 ml.) were heated under reflux for 9 hours. The liquid was steam-distilled, treated with charcoal, concentrated to small bulk, and cooled, whereupon the *chloride* separated (60% yield). It crystallised from alcohol in golden-yellow prisms, m. p. 225—226° (decomp.) (Found: N, 11·0; Cl, 9·3. $C_{19}H_{18}O_4N_3Cl$ requires N, 10·8; Cl, 9·2%). Hydrolysis at 150° with 70% sulphuric acid gave 6-amino-*p*-nitrobenzylquinolinium sulphate, converted into the iodide, m. p. 222°, identical with the substance already described. Catalytic reduction yielded 6-carbethoxyamino-*p*-aminobenzylquinolinium chloride, which was unstable; the derived acetyl derivative was stable but a number of salts examined were gelatinous.

6-*Carbethoxyamino*-m-*nitrobenzylquinolinium chloride*, prepared in the same manner as the *p*-isomer, crystallised from alcohol in small, pale yellow rosettes, m. p. 220—221° (decomp.) (Found: C, 59·3; H, 4·6; N, 10·9; Cl, 9·1. $C_{19}H_{18}O_4N_3Cl$ requires C, 58·8; H, 4·7; N, 10·8; Cl, 9·2%).

6-*Carbethoxyamino*-m-*aminobenzylquinolinium Chloride*.—The above nitro-compound was reduced catalytically in dilute hydrochloric acid, and the filtrate evaporated to dryness to yield the *hydrochloride*, colourless crystals from methyl alcohol–ethyl acetate; m. p. 190—191° (decomp.) (Found: N, 10·8; Cl, 17·9. $C_{19}H_{21}O_2N_3Cl_2$ requires N, 10·65; Cl, 18·0%).* The aqueous solution remained unchanged on addition of sodium acetate and boiling.

p-*Nitrobenzylisoquinolinium chloride*, prepared in the general manner in quantitative yield, formed long thin prisms from alcohol–ethyl acetate; m. p. 222° (Found: N, 9·3; Cl, 11·8. $C_{16}H_{13}O_2N_2Cl$ requires N, 9·3; Cl, 11·8%).*

p-*Aminobenzylisoquinolinium chloride* was obtained as yellow crystals (m. p. 94—95°) by reduction of the above nitro-compound. It decomposed rapidly in warm water, liberating *iso*quinoline, and could not be recrystallised. The acetamido-compound was stable, giving an *iodide*, m. p. 203°, colourless prisms from methyl alcohol (Found: C, 53·5; H, 4·0; N, 6·8; I, 31·5. $C_{18}H_{17}ON_2I$ requires C, 53·5; H, 4·2; N, 6·9; I, 31·4%).

m-*Nitrobenzylisoquinolinium chloride* formed fine colourless needles from alcohol; m. p. 224—225° (yield 92%) (Found: N, 9·45; Cl, 11·9%).*

m-Aminobenzyl*iso*quinolinium chloride was stable in hot aqueous solution; the *hydrochloride* formed small rosettes of buff-coloured needles from methyl alcohol–ethyl acetate, m. p. 238° (Found: N, 8·9; Cl, 23·0. $C_{16}H_{16}N_2Cl_2$ requires N, 9·1; Cl, 23·1%).

p-Nitrobenzylpyridinium chloride obtained in 80% yield, formed colourless prisms from alcohol–ethyl acetate; m. p. 207° (Found: N, 11·3; Cl, 14·4. Calc. for $C_{12}H_{11}O_2N_2Cl$: N, 11·2; Cl, 14·2%). Grainger (*Chem. News*, 1923, **126**, 182) gave m. p. 208°; Jacobs and Heidelberger (*J. Biol. Chem.*, 1915, **20**, 667) gave m. p. 204—207°; Lellmann and Pekrun (*loc. cit.*) described a much lower-melting form which is probably a hydrate.

p-Aminobenzylpyridinium chloride, by catalytic reduction of the above nitro-compound in dilute hydrochloric acid, formed a hydrochloride, m. p. 195—196°, colourless plates from methyl alcohol–ethyl acetate (Found: N, 10·8; Cl, 27·4. Calc. for $C_{12}H_{14}N_2Cl_2$: N, 10·9; Cl, 27·6%). Lellmann and Pekrun (*loc. cit.*) gave m. p. 183—185°. The aqueous solution was unchanged on addition of sodium acetate, but, on boiling, decomposition gave pyridine and a brown amorphous material; mere boiling of an aqueous solution of the hydrochloride brought about some decomposition, as shown by cooling and addition of sodium acetate.

m-Nitrobenzylpyridinium chloride, obtained in nearly quantitative yield, formed long needles from alcohol–ethyl acetate, m. p. 194° (Found: N, 10·8; Cl, 14·15%). Lellmann and Pekrun (*loc. cit.*) described a hydrate, m. p. 100°, and Kröhnke (*Ber.*, 1938, **71**, 2583) a solvate, m. p. 191°.

m-Aminobenzylpyridinium chloride was stable in boiling aqueous solution. The hydrochloride formed long, colourless needles from methyl alcohol–ethyl acetate; m. p. 222—223° (Found: N, 10·8; Cl, 27·6%). Lellmann and Pekrun (*loc. cit.*) gave m. p. *ca.* 220°.

Phenyldimethyl-*p*-nitrobenzylammonium chloride, from the components in boiling aqueous suspension, formed stout prisms from alcohol–ethyl acetate; m. p. 111—112° (Found: N, 9·45; Cl, 12·0. Calc. for $C_{15}H_{17}O_2N_2Cl$: N, 9·6; Cl, 12·1%) (Wedekind, *Annalen*, 1899, **307**, 287, gave m. p. 118—120°). On reduction in dilute hydrochloric acid with palladised charcoal, 8 atoms of hydrogen were absorbed; addition of sodium acetate and acetic anhydride followed by steam-distillation separated the product into dimethylaniline (picrate, m. p. 162°) and acet-*p*-toluidide (mixed m. p.). Reduction with warm neutral ferrous hydroxide gave a copious yield of dimethylaniline (picrate, m. p. 162°) as the only identifiable product.

Phenyldimethyl-*m*-nitrobenzylammonium chloride, colourless prisms from alcohol–ethyl acetate, had m. p. 151—152° (Found: N, 9·6; Cl, 12·4%). Peacock (*J. Soc. Dyers Col.*, 1926, **42**, 53) gave m. p. 144°.

Catalytic reduction and working up as described for the *p*-isomer gave dimethylaniline (picrate, m. p. 162°) and aceto-*m*-toluidide (mixed m. p.).

Phenyldimethyl-m-*aminobenzylammonium chloride*, formed when the above nitro-compound was reduced with warm neutral ferrous hydroxide, was stable in boiling aqueous solution. It was characterised as the dipicrate, long orange-yellow prisms from acetic acid; m. p. 159—160° (Found: C, 47·55; H, 3·1; N, 17·0. $C_{27}H_{22}O_{14}N_8$ requires C, 47·5; H, 3·2; N, 16·4%).

8-*Methoxy*-m-*nitrobenzylquinolinium chloride*, from its components in boiling aqueous suspension

(24 hours, 53%), formed pale yellow prisms from alcohol–ethyl acetate; m. p. 157—158° (Found: N, 8·5; Cl, 11·2. $C_{17}H_{15}O_3N_2Cl$ requires N, 8·5; Cl, 10·8%).

The author is indebted to Messrs. Bennett and MacMurray for the micro-analyses and to Mr. D. Armitage for technical assistance.

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444. *Hydroxylation of Nitrobenzene.*

By (MISS) H. LOEBL, G. STEIN, and J. WEISS.

The hydroxylation of nitrobenzene has been carried out at room temperature by the action of hydroxyl radicals produced by the hydrogen peroxide–ferrous salt reaction (Haber and Weiss, *Proc. Roy. Soc.*, 1934, *A*, **147**, 332). It has been found that under these conditions *o*-, *p*-, and *m*-nitrophenols are formed, the relative quantities of which have been determined. *mm'*-Dinitrodiphenyl has also been isolated as one of the by-products of the reaction. These results are in agreement with a free-radical mechanism of hydroxylation.

MANY theoretical considerations have been published regarding the orientation of substituents in the aromatic nucleus, mainly on substitution by electrophilic, nucleophilic, and also by free-radical reagents (cf. Ingold, *Ann. Reports*, 1926, **23**, 112; 1927, **24**, 106; *Chem. Reviews*, 1934, **15**, 225; Hey, *Ann. Reports*, 1940, **37**, 282; Wheland, "The Theory of Resonance," New York and London, 1947).

However, very limited experimental evidence is available regarding substitution by free radicals in the monosubstituted aromatic nucleus, particularly quantitative data, with the exception of some recent work in which it was found that substitution by aryl radicals takes place at all three positions with respect to CO_2Et (Hey, *J.*, 1934, 1966) and Cl and Br (France, Heilbron, and Hey, *J.*, 1938, 1364).

It is known that the system hydrogen peroxide–ferrous salt produces hydroxyl radicals by the reaction $Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH$ (Haber and Weiss, *loc. cit.*; Baxendale, Evans, and Park, *Trans. Faraday Soc.*, 1946, **42**, 155).

It seemed to be of interest, therefore, to investigate the action of the hydroxyl radicals produced by this and by other means (Stein and Weiss, *Nature*, 1948, **161**, 650) on simple aromatic compounds. We have so far investigated the action on benzene, phenol, benzoic acid, and nitrobenzene. The case of nitrobenzene which offers a number of interesting points is now reported.

It is to be expected that the nitro-group removes electrons from the carbon atom to which it is attached and thus increases its electron affinity. As a result of this, substitution by the common electrophilic reagents takes place in the *m*-position, whereas nucleophilic reagents would be expected to attack the *o*- and *p*-positions although with greater difficulty. With regard to free radicals, it remained to be seen whether the strong directive influence of the nitro-group has some effect or whether substitution takes place in all three positions and to determine the relative abundance of the isomers formed.

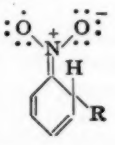
We found that, in spite of the well-known comparative resistance of nitrobenzene to further oxidation, hydroxylation of nitrobenzene proceeded with great ease under suitable conditions even at room temperature, and that the products of the reaction are further attacked, leading to the formation of polyphenolic compounds. In order to restrict the attack to the first stages and thus to get some idea of the relative proportions of the monohydroxylated isomers, we had to work at low pH's and to use a large excess of nitrobenzene so that only a relatively small portion of it was converted and thus further attack on the primary reaction products was inhibited.

The reaction was carried out by allowing dilute solutions of ferrous sulphate and hydrogen peroxide to drop simultaneously into a well-stirred mixture of nitrobenzene and water. Under these conditions all three isomeric nitrophenols could be isolated from the reaction mixture in the approximate proportions *o*- 0·56, *p*- 1·0, *m*- 0·44.

It will be seen that, in spite of the fact that of the five available positions in which substitution can occur only one is *p*-, the amount of the *p*-isomer is considerably greater than that of the *o*- or the *m*-isomer. This cannot be due in this case to the ease of its isolation, as the *o*-isomer can be isolated at least as easily. The *m*-isomer is clearly not favoured in this case, as its proportion is about 20% of the total amount, this being only about half the amount to be expected on purely statistical grounds. Furthermore, steric hindrance does not seem to

prevent the formation of the *o*-isomer, which is produced in larger quantity than the *m*-compound.

The result is in general agreement with those of earlier workers (*locc. cit.*) and with the theoretical considerations of Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900), *viz.*, that any radical reagent should attack preferentially the *o*- and *p*-positions on account of (i) the greater availability of an unpaired electron at the *o*- and *p*-positions, (ii) the fact that the quinonoid resonance structures for the *o*- and *p*-transition states (I, II) are more stable than the corresponding one for the *m*-substitution (III).



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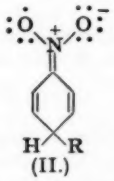

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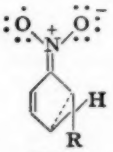

(III.)

It has been possible also to isolate a small quantity of *m*-dinitrodiphenyl from the reaction mixture, indicating that free nitrophenyl radicals are formed in the reaction. The fact that only this dimer has been isolated in a pure state does not exclude the possibility of other isomers also being formed in the reaction. We will discuss the mechanism of these reactions in subsequent papers, but the results reported above indicate that the hydroxylation of nitrobenzene by the ferrous–hydrogen peroxide reagent proceeds by a free-radical mechanism. It is somewhat remarkable and of some interest that the hydroxylation of the relatively inert nitrobenzene—which frequently requires extreme conditions and high temperatures to become reactive—proceeds in this case with ease at room temperature, as is often the case in free-radical reactions.

Experimental.

(All m. p.s are uncorrected.)

Freshly steam-distilled nitrobenzene (5 g.) was mixed with sulphuric acid (150 ml.; 2N.), and 4-vol. hydrogen peroxide (100 ml.) and ferrous sulphate solutions (100 ml., 2%) were added with stirring during 45 minutes. If the solution is neutral or less acid or the peroxide is added more rapidly, a dark mixture of polyphenolic nature results. However, if the process is carried out as above, a pale yellow liquid results, the nitrobenzene layer having only a slightly deeper orange colour. The total amount of nitrophenols formed is about 150 mg. The reaction mixture was extracted exhaustively with ether, the extracts of several runs united, washed with dilute acid and water, and extracted exhaustively with dilute sodium hydroxide, and the alkaline extracts acidified immediately. The acid solution was extracted with benzene, and the extract dried ($CaCl_2$), boiled for 1—2 minutes with charcoal, and filtered. For further separation Karrer and Nielsen's method of chromatography (*Zangger Festschrift*, 1934, 954) was tried but good results were obtained by the following simple procedure.

The benzene solution was once more extracted with dilute sodium hydroxide and the alkaline extract steam-distilled. When the distillate was free from organic material, the solution was acidified and further steam-distilled in the micro-steam-distilling apparatus. The *o*-nitrophenol crystallised from the distillate in yellow prisms, m. p. 44°, mixed m. p. 44°. The residual solution is extracted with ether, the ether extract was dried and evaporated, and a few drops of 10% sodium hydroxide were added to the residue. The sodium salt of *p*-nitrophenol, which is nearly insoluble in 10% sodium hydroxide, was precipitated and filtered off. The alkaline solution containing the *m*-isomer was acidified and extracted with ether, and the extract on evaporation yielded the *m*-nitrophenol.

The sodium salt of *p*-nitrophenol was dissolved in very little hot water and acidified; long colourless needles of *p*-nitrophenol crystallised overnight, giving m. p. and mixed m. p. 114°. The *m*-isomer, obtained as above, had m. p. *ca.* 84°. One recrystallisation from hot dilute hydrochloric acid gave crystals, m. p. and mixed m. p. 94°. The relative amounts of the isomers in several experiments were within the following limits: *o*-, 25—30; *p*-, 50—55; *m*-, 20—25%.

A part of the reaction products was neither volatile with steam nor soluble in dilute alkali, and yielded a dark precipitate when the reaction mixture was basified; this was filtered off, washed with water, dried, and then sublimed in a vacuum, forming yellow crystals, m. p. 170—180°, which on recrystallisation from absolute alcohol yielded colourless crystals, m. p. 198°, corresponding to the reported m. p. of *mm'*-dinitrodiphenyl (Found: C, 59·2; H, 3·0. Calc. for $C_{12}H_8O_4N_2$: C, 59·2; H, 3·3%). The mixed m. p. with an authentic specimen was 198°.

The yellow alcoholic mother-liquor from the recrystallisation, on slow dilution with water, gave a very small yield of pale yellow crystals, m. p. 100°, which is possibly another dinitrodiphenyl.

Part of the experimental work was carried out by one of us (H. L.) whilst at the Université Libre, Brussels, and our thanks are due to Professor Martin for his hospitality and interest. We also thank Professor G. R. Clemo for his interest in this work.

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445. *The Reactions of Organic Peroxides. Part I. 2-Phenyl-2-butyl Hydroperoxide.*

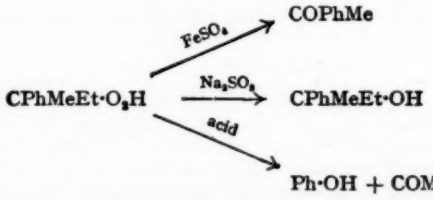
By E. G. E. Hawkins.

2-Phenyl-2-butyl hydroperoxide has been prepared in good yield by the emulsion oxidation of *sec.*-butylbenzene. Reaction of the hydroperoxide with ferrous sulphate yields acetophenone, with sodium sulphite it gives phenylmethylethylcarbinol, whilst mineral acid causes formation of methyl ethyl ketone and phenol.

The preparation of 2-phenyl-2-butyl hydroperoxide by oxidation of *sec.*-butylbenzene in the homogeneous liquid phase in ultra-violet light has recently been reported by Ivanov *et al.* (*Doklady Akad. Nauk. S.S.S.R.*, 1948, **59**, 905); the crude oxidate appeared to contain 5—6% of hydroperoxide.

Following the method used for the oxidation of *iso*propylbenzene and *sec.*-butyltoluene (the method developed by Armstrong, Hall, and Quin, *Nature*, 1949, in the press; The Distillers Company Ltd., B.P. 610,293), *sec.*-butylbenzene has now been oxidised in emulsion to yield a crude product containing *ca.* 30% of hydroperoxide. The oxidate was extracted with concentrated aqueous alkali, but only part of the hydroperoxide could be remove by this means. From the alkaline solution the hydroperoxide was obtained by treatment with carbon dioxide followed by benzene extraction.

The purified, distilled hydroperoxide had physical properties very similar to those given by the Russian authors, and its reaction with ferrous sulphate gave rise mainly to acetophenone as described by them.



Sodium sulphite reduced the hydroperoxide to phenylmethylethylcarbinol, whilst treatment with mineral acid brought about fission of a carbon–carbon linkage to give phenol and methyl ethyl ketone. This reaction is similar to that described for 2-phenyl-2-propyl hydroperoxide by Hock and Lang (*Ber.*, 1944, **77**, *B*, 257) in which phenol and acetone were formed.

Experimental.

(All m. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss.)

sec.-*Butylbenzene*.—This was prepared by alkylation of benzene with but-1-ene (obtained by dehydration of *n*-butanol with alumina at 400°; cf. Pines, *J. Amer. Chem. Soc.*, 1933, **55**, 3892) in the presence of sulphuric acid as catalyst (Corson and Pines, *ibid.*, 1936, **58**, 919). The mixture was kept at about 10° and only $\frac{1}{3}$rd of the stoicheiometric quantity of butene was used, so as to keep di-substitution at a minimum. The fraction finally taken had b. p. 172—175°/764 mm., n_D^{20} 1·4898.

Oxidation of sec.-*Butylbenzene*.—(i) The hydrocarbon (130 g., 150 c.c.), water (300 c.c.), sodium carbonate (3 g.), and stearic acid (0·25 g.) were stirred at 85°, and a slow stream of oxygen passed through the solution. Reaction was slow and at an average rate of absorption of 350 c.c. of oxygen per hour the concentration of hydroperoxide reached 30% (on the oil phase) in about 120 hours. The peroxide content, as determined by potassium iodide–acetic acid reagent, began to fall again after this time.

The organic layer was separated from the aqueous phase, and extracted three times with strong aqueous sodium hydroxide. The hydroperoxide was obtained from the combined alkaline extracts by passage of carbon dioxide and extraction with benzene, followed by evaporation of the benzene under reduced pressure in an atmosphere of nitrogen. Distillation of the residue yielded an initial small fraction of acetophenone, identified as its 2 : 4-dinitrophenylhydrazone, followed by the main fraction (5 g.), b. p. 60°/1·5 × 10^{-2} mm. This fraction contained 61·5% of hydroperoxide (determined iodometrically).

The material remaining after alkali extraction of the organic layer still contained much peroxide and was distilled directly to give unreacted hydrocarbon (51·1 g.) as well as the following fractions: (*a*) (12·9 g.), b. p. 56—58°/3 × 10^{-2} mm. (containing acetophenone and 30% of hydroperoxide); (*b*) (9·0 g.), b. p. 58—66°/3 × 10^{-2} mm. (containing 66% of hydroperoxide); and (*c*) (13·5 g.), b. p. 66—68°/3 × 10^{-2} mm. (containing 89% of hydroperoxide).

(ii) *sec.*-Butylbenzene was hydrogenated over Raney nickel at atmospheric pressure to saturate traces of material having olefinic side-chains. Using quantities and conditions of oxidation as before a concentration of 25% of hydroperoxide (on the organic phase) was reached in only 47 hours. The organic layer was separated and distilled directly, giving fractions similar to those described in (i).

2-*Phenyl*-2-*butyl Hydroperoxide*.—A portion of the peroxide concentrate was dissolved in light

petroleum (b. p. 40—60°) and treated with 45% sodium hydroxide solution. The solid sodium salt of the hydroperoxide was filtered off and washed with petroleum, and from it the free hydroperoxide was regenerated by treatment of an aqueous suspension with carbon dioxide. Distillation gave material, b. p. 58—58·5°/0·01 mm., n_D^{20} 1·5206 (Found: C, 72·6, 72·7; H, 8·71, 8·83%; peroxide equivalent, 162. Calculated for $C_{10}H_{14}O_3$: C, 72·3; H, 8·43%; peroxide equivalent, 166).

Reaction with ferrous sulphate. The hydroperoxide (5 g.) was stirred with ferrous sulphate solution (10 g. of crystalline salt in 20 c.c. of water) for one hour at water-bath temperature. The solution, which contained a brown precipitate of a ferric compound, was extracted with ether, the ethereal extract was evaporated, and the residue (3·9 g.) distilled. Acetophenone, b. p. 200—204°, was the only product (the 2 : 4-dinitrophenylhydrazone had m. p. 244—245°, unaltered by admixture with an authentic specimen).

Reaction with sodium sulphite. The hydroperoxide (5 g.) and sodium sulphite (10 g. in 20 c.c. of water) were stirred for 3—4 hours on the water-bath. On extraction of the product with ether, followed by removal of the solvent and distillation, only phenylmethylethylcarbinol, b. p. 53—54°/0·1 mm. (4·0 g.), was obtained.

This yielded a *phenylurethane*, m. p. 89—90° (Found: C, 75·9; H, 7·29; N, 4·99. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·06; N, 5·20%), and an *α-naphthylurethane*, m. p. 129—130·5° (Found: C, 78·4; H, 6·27; N, 4·71. $C_{21}H_{21}O_2N$ requires C, 78·99; H, 6·58; N, 4·39%).

Reaction with mineral acid. The hydroperoxide (10 g.) and sulphuric acid (10%; 50 c.c.) were stirred for 4 hours on the water-bath. After removal of the solvent from the ethereal extract of the solution, distillation gave: fraction 1 (1·0 g.), b. p. 70—80°; fraction 2 (0·6 g.), b. p. 80—165°; fraction 3 (5·8 g.), b. p. 165—185°; and residue (0·3 g.).

Fraction 1 was methyl ethyl ketone (2 : 4-dinitrophenylhydrazone, m. p. 115—116° unchanged on admixture with a synthetic sample). Fraction 2 contained both methyl ethyl ketone and phenol. Fraction 3 consisted of phenol (benzoate, m. p. and mixed m. p. 69—70°).

The author thanks his colleagues for discussions and in particular Dr. D. C. Quin and Dr. R. H. Hall for details of the method of emulsion oxidation.

THE DISTILLERS CO., LTD., RESEARCH AND DEVELOPMENT DEPT.,
GREAT BURGH, EPSOM. [*Received, April 8th*, 1949.]

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446. *The Effect of Hydrazine on the Condensation of Certain α-Ketols and Related Substances with 2 : 4 : 5-Triamino-6-hydroxypyrimidine.*

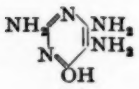
By H. S. FORREST and JAMES WALKER.

An earlier study of the effect of hydrazine on the condensation of 2 : 4 : 5-triamino-6-hydroxypyrimidine (I) with glucose and fructose has been extended to the condensation of (I) with acetol, methylglyoxal, dihydroxyacetone, and *p*-tolyl-D-*iso*glucosamine.

THE appearance of a communication by Karrer and Schwyzer (*Helv. Chim. Acta*, 1949, **32**, 423) makes it desirable for us to submit immediately an account of experiments * carried out as an extension of work previously described (Forrest and Walker, *Nature*, 1948, **161**, 308; this vol., p. 79). In our previous communications it was shown that 2 : 4 : 5-triamino-6-hydroxypyrimidine (I) reacts with glucose and fructose in the presence of hydrazine to give in both cases 2-amino-4-hydroxy-6-D-*arabo*tetrahydroxybutylpteridine (II). In the absence of hydrazine, glucose and (I) afford the isomeric 2-amino-4-hydroxy-7-D-*arabo*tetrahydroxybutylpteridine (III) (cf. also Karrer, Schwyzer, Erden, and Siegwart, *Helv. Chim. Acta*, 1947, **30**, 1031), which, in the light of subsequent events (see below), may have contained some 2-amino-4-hydroxy-7-D-*erythro*-2′ : 3′ : 4′-trihydroxybutylpteridine (IV), whilst glucosone and (I) afford (II) in the presence of hydrazine and (III) in its absence (this vol., p. 79). The results obtained in the presence of hydrazine were interpreted in terms of an open-chain osazone-type of derivative formed from the sugar component and hydrazine before interaction with (I), otherwise, had the reaction been initiated by condensation between the sugars and (I) before the participation of hydrazine, the hydrazine could not have exerted a controlling influence over the orientation, and the production of the same product (II) from glucose and fructose would have been impossible. Weygand and Bergmann (*Chem. Ber.*, 1947, **80**, 255; cf. also Weygand, *Ber.*, 1940, **73**, 1268) have proposed a mechanism for Ohle and Hielscher's synthesis of 2-D-*arabo*tetrahydroxybutylquinoxaline (V) (*Ber.*, 1941, **74**, 13) from *o*-phenylenediamine and glucose in the presence of hydrazine in which *o*-phenylenediaminemonoglucoside is produced initially, thus determining the orientation, and then undergoes Amadori rearrangement to *o*-aminophenyl*iso*glucosamine before the participation of hydrazine and ring-closure to (V).

* Apart from the experiments with *p*-tolyl*iso*glucosamine the work described in the present communication was completed by September 1948, when this collaboration ended with the departure of one of the authors (H. S. F.) to another laboratory.—J. W.

The equivalence of the two amino-groups in *o*-phenylenediamine obscures the issue in the case considered by Weygand and Bergmann, but their mechanism is untenable in view of the above observations and also in the light of the results presented in this communication.



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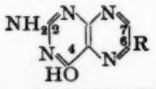
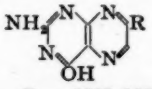


(II; R = $[CH\cdot OH]_3\cdot CH_2\cdot OH$.)
(VII; R = CH_3.)
(IX; R = CO_2H.)
(X; R = $CH_2\cdot OH$.)
(XI; R = $CH_2\cdot[CH\cdot OH]_2\cdot CH_2\cdot OH$.)



(III; R = $[CH\cdot OH]_3\cdot CH_2\cdot OH$.)
(IV; R = $CH_2\cdot[CH\cdot OH]_2\cdot CH_2\cdot OH$.)
(VI; R = CH_3.)
(VIII; R = CO_2H.)

The open-chain formulation of sugar osazones used by Fischer has been supported by Engel (*J. Amer. Chem. Soc.*, 1935, **57**, 2419) and by Chargaff and Magasanik (*ibid.*, 1947, **69**, 1459), and although Haworth (" The Constitution of Sugars," 1929, p. 7) has suggested the possibility of cyclic structures, no final conclusions have been reached (cf. Percival, *Advances in Carbohydrate Chemistry*, 1948, **3**, 23). As the interpretation of our previous results was based on an acyclic osazone-type of structure, it was deemed desirable to extend our study of the effect of hydrazine to condensations involving α-ketols which could form only acyclic osazones. The first case studied was the condensation of (I) with acetol, wherein the product of direct condensation unexpectedly proved to be 2-amino-4-hydroxy-7-methylpteridine (VI); apparently, Karrer and Schwyzer (*loc. cit.*) observed practically no direct condensation between acetol and (I). As condensation reactions of (I) with hydroxycarbonyl compounds are undoubtedly initiated between the nucleophilic 5-amino-group and the electrophilic carbonyl carbon atom (cf. this vol., pp. 79, 2002), the formation of (VI) from acetol must be ascribed to the equilibrium between acetol and lactaldehyde, only the latter undergoing reaction readily with (I). Ordinarily this equilibrium lies far on the side of acetol, as indicated by its production in reactions expected to yield lactaldehyde (Nef, *Annalen*, 1904, **335**, 265; Wohl, *Ber.*, 1908, **41**, 3609; Wohl and Lange, *ibid.*, p. 3612; Hildesheimer, *ibid.*, 1910, **43**, 2804; cf. also Goto, *Bull. Chem. Soc. Japan*, 1940, **15**, 103). When the reaction was repeated with the addition of hydrazine, 2-amino-4-hydroxy-7-methylpteridine (VI) was again produced, apparently exclusively; under comparable conditions Karrer and Schwyzer (*loc. cit.*) claim the formation of the isomeric 2-amino-4-hydroxy-6-methylpteridine (VII). If, however, acetol and hydrazine were set aside together in dilute acetic acid for varying periods of time before the addition of (I), a mixture of 2-amino-4-hydroxy-7- (VI) and 2-amino-4-hydroxy-6-methylpteridine (VII) was obtained, the former predominating; these two substances are not readily separated, but the sodium salts of the mixture of carboxylic acids obtained on alkaline permanganate oxidation were readily separated into the less soluble sodium salt of 2-amino-4-hydroxypteridine-7-carboxylic acid (VIII) and the sodium salt of 2-amino-4-hydroxypteridine-6-carboxylic acid (IX), which are easily characterised by means of their ultra-violet absorption spectra and fluorescence characteristics. As this only partial reversal of the orientation in the presence of hydrazine could be ascribed to the incompleteness of osazone formation between acetol and hydrazine, this difficulty was readily overcome by allowing methylglyoxal to react with hydrazine before admixture with (I); under these conditions the product was 2-amino-4-hydroxy-6-methylpteridine (VII), the orientation being established by oxidation to 2-amino-4-hydroxypteridine-6-carboxylic acid (IX). It will be recalled that the direct reaction between methylglyoxal and (I) affords 2-amino-4-hydroxy-7-methylpteridine (VI) (Mowat *et al.*, *Ann. N.Y. Acad. Sci.*, 1946, **48**, Art. 5, 279; Forrest and Walker, this vol., p. 79), although Karrer and Schwyzer (*loc. cit.*) are of the opinion that the product also contains some 2-amino-4-hydroxy-6-methylpteridine. It is therefore clear, as indicated previously (this vol., p. 79), that condensation in the presence of hydrazine does not proceed by way of the keto-aldehyde (osone) as an intermediate as Ohle and Hielscher (*loc. cit.*) and Karrer and Schwyzer (*Helv. Chim. Acta*, 1948, **31**, 783) have claimed. Karrer and Schwyzer (*ibid.*, 1949, **32**, 429) have now also recognised that the keto-aldehyde cannot be an intermediate.

We then examined the condensation of dihydroxyacetone with (I). This condensation was first mentioned by Karrer, Schwyzer, Erden, and Siegwart (*loc. cit.*), who gave no experimental details and stated in a footnote that the product of this reaction was first isolated in the laboratories of F. Hoffmann-La Roche and Co. in Basle; the product, whatever the experimental conditions used in its preparation, was clearly taken to be 2-amino-4-hydroxy-6-hydroxymethylpteridine (X), and it was subsequently used in a reaction with *p*-aminobenzoylglutamic

acid yielding a product claimed to contain 15% of folic acid, as shown by biological assay (Karrer and Schwyzer, *ibid.*, 1948, **31**, 777). Shortly afterwards, Angier *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 3029) pointed out, on the basis of the wealth of experience accumulated by their group in this field, that the reaction of (I) with any three-carbon compound which might be expected to produce initially a hydroxymethyl- or halogenomethyl-dihydropteridine, actually gave primarily the fully aromatised methylpteridine with no substituent on the methyl group; thus (I) afforded 2-amino-4-hydroxy-7-methylpteridine (VI) on condensation with each of the following substances: 1 : 3-dichloroacetone, βγ-dichloropropaldehyde, α-bromotetronic acid, and DL-glyceraldehyde. They therefore inferred that the product obtained by Karrer, Schwyzer, Erden, and Siegwart (*loc. cit.*) from (I) and DL-glyceraldehyde, for which poor analytical results were obtained, was likewise 2-amino-4-hydroxy-7-methylpteridine (VI) and not 2-amino-4-hydroxy-7(or -6?)-hydroxymethylpteridine. Still later, Weygand, Wacker, and Schmied-Kowarzik (*Experientia*, 1948, **4**, 427) reported that diacetoxyacetone and (I) afforded either 2-amino-4-hydroxy-6- (VII) or 2-amino-4-hydroxy-7-methylpteridine (VI), and not 2-amino-4-hydroxy-6-hydroxymethylpteridine (X); furthermore, Weygand *et al.* repeated Karrer and Schwyzer's condensation of diaminoacetone dihydrochloride with (I) and obtained 2-amino-4-hydroxy-7-methylpteridine (VI), whereas Karrer and Schwyzer (*Helv. Chim. Acta*, 1948, **31**, 777) stated that their product was not the expected 2-amino-4-hydroxy-6(?)-aminomethylpteridine but, on the basis of the analytical evidence, 2-amino-4-hydroxy-7(?)-hydroxymethylpteridine. Weygand *et al.* (*loc. cit.*) also obtained either 2-amino-4-hydroxy-6- (VII) or 2-amino-4-hydroxy-7-methylpteridine (VI) from the condensation of 1 : 3-bis-(*p*-carboxy-*N*-formanilido)acetone with (I). In our hands the direct condensation of dihydroxyacetone with (I) has afforded 2-amino-4-hydroxy-7-methylpteridine (VI), although a small proportion of the product consisted of a 2-amino-4-hydroxypteridine substituted in the 6-position, as a trace of 2-amino-4-hydroxypteridine-6-carboxylic acid (IX) appeared in the carboxylic acid obtained on oxidation of the crude reaction product with alkaline potassium permanganate; this result is in general accord with the observations of Angier *et al.* (*loc. cit.*) and of Weygand *et al.* (*loc. cit.*), but it is at variance with Karrer and Schwyzer's claim (*Helv. Chim. Acta*, 1949, **32**, 423) that 2-amino-4-hydroxy-6-methylpteridine (VII) is the product of the direct condensation between dihydroxyacetone and (I). When dihydroxyacetone was treated in the cold with hydrazine and then added to (I), the product was 2-amino-4-hydroxy-6-hydroxymethylpteridine (X), affording 2-amino-4-hydroxypteridine-6-carboxylic acid (IX) on oxidation. Karrer and Schwyzer (*ibid.*) have now purified their earlier product from dihydroxyacetone and (I), and state it to be 2-amino-4-hydroxy-6-hydroxymethylpteridine (X); this product is now, for the first time, said to have been prepared in the presence of hydrazine.

Weygand, Wacker, and Schmied-Kowarzik (*loc. cit.*) have reported that the condensation of *p*-tolyl-D-*iso*glucosamine with (I) affords 2-amino-4-hydroxy-7-D-*erythro*-2′ : 3′ : 4′-trihydroxybutylpteridine (IV) and not the expected *tetra*hydroxybutylpteridine, but no details have yet become available.* We have also investigated this reaction and have ascertained the effect of hydrazine upon the course of the condensation. The direct condensation of *p*-tolyl-D-*iso*glucosamine with (I) afforded a product having initially $[\alpha]_D^{22.5}$ −69° in N-hydrochloric acid. On repeated recrystallisation the optical rotation progressively fell and appeared to become constant at $[\alpha]_D^{18}$ −22°, by which time the substance gave acceptable analytical figures for 2-amino-4-hydroxy-7- (IV) or 2-amino-4-hydroxy-6-D-*erythro*-2′ : 3′ : 4′-trihydroxybutylpteridine (XI). Oxidation of the material from the last recrystallisation afforded a mixture of acids, which was separated, *via* the sodium salts, into 2-amino-4-hydroxypteridine-7-carboxylic acid (VIII), giving acceptable analytical figures and showing the characteristic fluorescence and absorption spectrum of this acid, and 2-amino-4-hydroxypteridine-6-carboxylic acid (IX); the analytical results for the latter acid were less satisfactory, but the fluorescence characteristics were unmistakable and the absorption spectrum agreed in every detail with that of the authentic substance. Both 2-amino-4-hydroxy-7- (IV) and 2-amino-4-hydroxy-6-D-*erythro*-2′ : 3′ : 4′-trihydroxybutylpteridine (XI) are therefore formed in the direct condensation of *p*-tolyl-D-*iso*glucosamine with (I). In sharp contrast, condensation of *p*-tolyl-D-*iso*glucosamine with (I) in the presence of hydrazine afforded 2-amino-4-hydroxy-6-D-

* *Note added*, 23.7.49.—Since this paper was submitted, a further communication by Weygand, Wacker, and Schmied-Kowarzik has come to hand (*Chem. Ber.*, 1949, **82**, 25). These authors purified their product from the direct condensation of *p*-tolyl-D-*iso*glucosamine and (I) by precipitation from dilute ammonia solution (charcoal) and crystallisation from water, and record $[\alpha]_D^{20}$ −46° in 0·1N-sodium hydroxide. Moreover, they also carried out this condensation in the presence of hydrazine and record $[\alpha]_D^{20}$ −88·5° and −83·6° in 0·1N-sodium hydroxide for (II), in good agreement with our values of −86·6°, −81·5°, and −83°, observed in N-hydrochloric acid.

*arabo*tetrahydroxybutylpteridine (II), having $[\alpha]_D^{22}$ −83° in N-hydrochloric acid, in good agreement with our previously recorded values (*locc. cit.*). One crystallisation sufficed to give a pure product affording 2-amino-4-hydroxypteridine-6-carboxylic acid (IX) on oxidation.

The direct condensation of (I) with sugars was first reported by Karrer, Schwyzer, Erden, and Siegwart (*Helv. Chim. Acta*, 1947, **30**, 1031) while we were engaged in a similar study. The use of hydrazine in this condensation, following Ohle and Hielscher's work (*loc. cit.*) with *o*-phenylenediamine, and the recognition of its influence were first reported from this laboratory [Forrest and Walker, *Nature*, 1948, **161**, 308; cf. also this vol., p. 79 (MS. received by the Society on 5.1.48)]. The only other application, to our knowledge, of hydrazine in the pteridine field is contained in the latest paper of Karrer and Schwyzer [*Helv. Chim. Acta*, 1949, **32**, 423 (MS. dated 28.1.49)], which has just come to hand and where they also state: "Leider hatten wir es in unseren früheren Mitteilungen auch unterlassen, darauf hinzuweisen, dass die von uns dargestellten Pteridin-Präparate aus 2,4,5-Triamino-6-oxypyrimidin und Glycerinaldehyd bzw. Dioxyacetone nicht alle in gleicher Weise gewonnen worden sind: einige unter Zusatz von Hydrazin, andere ohne diesen Zusatz. Es hat sich nunmehr gezeigt, dass dadurch auch die Natur der Reaktionsprodukte in einem gewissen Ausmass beeinflusst wird." The necessity for this rectification and the conclusion drawn from it had obviously not been appreciated at the time of their comment [*ibid.*, 1948, **31**, 782 (MS. dated 22.3.48)] on our preliminary note, when they interpreted our results with glucose and fructose in terms of glucosone as a common intermediate.

Experimental.

Direct Condensation of Acetol with 2 : 4 : 5-Triamino-6-hydroxypyrimidine. Formation of 2-Amino-4-hydroxy-7-methylpteridine (VI).—Acetol (5 c.c.) was added to a suspension of 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (18·3 g. in water (100 c.c.) containing sodium acetate (11 g., anhydrous), which was heated on the water-bath and stirred in a slow stream of nitrogen. After 5 hours on the boiling water-bath the suspension was cooled and the yellowish-brown solid (3 g.) was collected, washed, and dried. Crystallisation from 5N-sodium hydroxide afforded the sodium salt as pale yellow needles. The product, recovered from the sodium salt by acidification with acetic acid, was obtained as a pale yellow amorphous powder (Found, on material dried at 160° in a vacuum: C, 47·1; H, 4·0. Calc. for $C_7H_7ON_5$: C, 47·5; H, 4·0%).

The substance was shown to be 2-amino-4-hydroxy-7-methylpteridine (VI) and it was identical with the substance previously obtained from (I) and methylglyoxal under similar conditions (this vol., p. 79). Its absorption spectrum in 0·1N-sodium hydroxide showed maxima at 250 and 357 mμ., and oxidation in alkaline solution with potassium permanganate afforded 2-amino-4-hydroxypteridine-7-carboxylic acid, which was identified by its absorption spectrum in alkaline solution and by its fluorescence characteristics.

Effect of Hydrazine on the Condensation of Acetol with 2 : 4 : 5-Triamino-6-hydroxypyrimidine. Formation of 2-Amino-4-hydroxy-7-(VI) *and 2-Amino-4-hydroxy-6-methylpteridine* (VII).—A number of experiments were carried out allowing varying times of contact between acetol and hydrazine before reaction with 2 : 4 : 5-triamino-6-hydroxypyrimidine. The following is a typical experiment.

Freshly prepared and freshly distilled acetol (3 c.c.) was dissolved in 10% acetic acid (30 c.c.) and treated with 90% hydrazine hydrate (2·5 c.c.). After warming spontaneously to about 35°, the solution was kept at room temperature for 3 hours before being added to a mixture of 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (10 g.), sodium acetate trihydrate (8 g.), and boric acid (4 g.) in water (40 c.c.), which was stirred on the water-bath in a slow stream of nitrogen. The mixture was heated for 5½ hours, and a bright yellowish-brown product (3·3 g.) separated. It was shown to be a mixture of the 7- and the 6-methyl derivative by oxidation to a mixture of the 7- and the 6-carboxylic acid. The crude product (2 g.) was dissolved in N-sodium hydroxide (50 c.c.) and oxidised on the water-bath with excess of potassium permanganate for ½ hour. Excess of permanganate was destroyed with alcohol and, after removal of manganese dioxide, the product (1·9 g.), precipitated with acetic acid, was obtained as a canary-yellow powder after collection at the centrifuge, washing, and drying. The crude mixture of acids was boiled with 2N-sodium hydroxide (*ca.* 100 c.c.), and the solution was filtered from a small residue (90 mg.). On cooling, the sodium salt (1·46 g.) of 2-amino-4-hydroxypteridine-7-carboxylic acid (VIII) separated and was readily identified by its absorption spectrum and fluorescence characteristics. On concentration of the mother-liquors to about one-fourth of their bulk and cooling, the sodium salt (0·35 g.) of 2-amino-4-hydroxypteridine-6-carboxylic acid (IX) separated and was similarly identified. Acidification of the final mother-liquors with glacial acetic acid gave a small amount (70 mg.) of crude 2-amino-4-hydroxypteridine-6-carboxylic acid (IX).

Direct Condensation of Methylglyoxal with 2 : 4 : 5-Triamino-6-hydroxypyrimidine. Formation of 2-Amino-4-hydroxy-7-methylpteridine (VI).—See this vol., p. 79.

Effect of Hydrazine on the Condensation of Methylglyoxal with 2 : 4 : 5-Triamino-6-hydroxypyrimidine. Formation of 2-Amino-4-hydroxy-6-methylpteridine (VII).—A solution of methylglyoxal (1·2 g.) in water (20 c.c.) was treated with hydrazine hydrate (2 c.c.; 90%) and, after 25 minutes at room temperature, the mixture was added to a suspension of 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (4·6 g.) in water (50 c.c.) containing sodium acetate (2·75 g.; anhydrous) and boric acid (2 g.), which was stirred on the water-bath in a gentle stream of nitrogen for 4 hours. After cooling, the product (2·2 g.) was collected. After crystallisation as the sodium salt from 5N-sodium hydroxide the substance was recovered as a pale yellow amorphous powder (Found, on material dried at 160° in a vacuum; C, 47·4; H, 4·1. Calc. for $C_7H_7ON_5$: C, 47·5; H, 4·0%).

The substance was shown to be 2-amino-4-hydroxy-6-methylpteridine (VII); its absorption spectrum in 0·1N-sodium hydroxide solution showed maxima at 252 and 363—364 mμ., and oxidation in alkaline solution with potassium permanganate afforded 2-amino-4-hydroxypteridine-6-carboxylic acid (IX), which was identified by its absorption spectrum and fluorescence characteristics.

When methylglyoxal was added to a suspension of 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate in water containing sodium acetate, boric acid, and hydrazine hydrate, the product consisted essentially of 2-amino-4-hydroxy-7-methylpteridine (VI) with only a small proportion of the 6-methyl isomer (VII), owing to the rapid direct reaction between methylglyoxal and 2 : 4 : 5-triamino-6-hydroxypyrimidine.

Direct Condensation of Dihydroxyacetone with 2 : 4 : 5-*Triamino-6-hydroxypyrimidine. Formation of* 2-*Amino-4-hydroxy-7-methylpteridine* (VI).—To a solution of crude dihydroxyacetone (5 g.) (Underkofler and Fulmer, *J. Amer. Chem. Soc.*, 1937, **59**, 301), estimated by titration (Shaffer and Hartmann, *J. Biol. Chem.*, 1920, **45**, 365) to contain 85%, in water (60 c.c.) there were added 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (5·1 g.) and sodium acetate (2·5 g.; anhydrous), and the mixture was heated on the water-bath under nitrogen for 2 hours. After cooling, the crude product (2·5 g.) was collected, washed, and dried. Part of the crude product was set aside for oxidative degradation and the rest was purified through the sodium salt. The crude substance (2·25 g.) was dissolved in 2N-sodium hydroxide (33 c.c.), and the filtered solution was treated with an equal volume of filtered 50% sodium hydroxide solution. The crystalline material which separated was collected after chilling in the ice-chest, and the process was repeated. The product (1·05 g.) was recovered from the twice recrystallised sodium salt as a light-yellow powder (Found: C, 47·9; H, 3·8. Calc. for $C_7H_7ON_5$: C, 47·5; H, 4·0%).

The crude reaction product (0·25 g.) was oxidised in dilute sodium hydroxide solution with excess of potassium permanganate on the water-bath for 30 minutes, affording a crude acid (0·16 g.). Crystallisation from 2N-sodium hydroxide afforded the sodium salt (100 mg.) of 2-amino-4-hydroxypteridine-7-carboxylic acid (VIII), identified by its green fluorescence in aqueous solution and by the maximum in its absorption spectrum in 0·1N-sodium hydroxide at 258 mμ.; the mother-liquors, on acidification with acetic acid, afforded traces only of a precipitate, which showed a sky-blue fluorescence in 0·1N-sodium hydroxide and therefore contained some 2-amino-4-hydroxypteridine-6-carboxylic acid (IX).

Effect of Hydrazine on the Condensation of Dihydroxyacetone with 2 : 4 : 5-*Triamino-6-hydroxypyrimidine. Formation of* 2-*Amino-4-hydroxy-6-hydroxymethylpteridine* (X).—Hydrazine hydrate (2·3 c.c.; 90%) was added to an aqueous solution (20 c.c.) of crude dihydroxyacetone (3·5 g.), and the mixture was kept at room temperature for 30 minutes before being added to a suspension of 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (5·1 g.) in water (60 c.c.) containing sodium acetate (3·1 g.; anhydrous) and boric acid (2·4 g.). The resulting mixture was heated under nitrogen on the water-bath for 2 hours, and the product (2 g.) was thereafter collected, washed, and dried. The pure substance, 2-amino-4-hydroxy-6-hydroxymethylpteridine (X), separated from a large volume of water (charcoal) as a pale yellow powder (Found, on material dried at 160° in a vacuum: C, 43·4; H, 3·6; N, 35·7. Calc. for $C_7H_7O_2N_5$: C, 43·5; H, 3·6; N, 36·3%).

Oxidation with potassium permanganate in the usual way afforded 2-amino-4-hydroxypteridine-6-carboxylic acid (IX), identified by the blue fluorescence of its sodium salt in aqueous solution and by the maximum in its absorption spectrum in 0·1N-sodium hydroxide at 261—262 mμ.

Direct Condensation of p-*Tolyl*-D-iso*glucosamine with* 2 : 4 : 5-*Triamino-6-hydroxypyrimidine. Formation of* 2-*Amino-4-hydroxy-7-* (IV) *and* 2-*Amino-4-hydroxy*-6-D-erythro-2′ : 3′ : 4′-*trihydroxybutylpteridine* (XI).—A mixture of *p*-tolyl-D-*iso*glucosamine (19·8 g.) (Weygand, *Ber.*, 1940, **73**, 1269), 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (21 g.), sodium acetate trihydrate (22·5 g.), and boric acid (6 g.) in water (270 c.c.) was heated in a stream of nitrogen for 6 hours on the water-bath. A greyish-brown solid separated and some tarry material floated on the surface. The product was collected at the centrifuge, washed with acetone and alcohol until the washings were colourless, and then with ether, and dried, affording a buff-coloured powder (15 g.). The crude material was dissolved in N-hydrochloric acid (240 c.c.), and some black insoluble material was separated. The dark brown solution was treated twice with charcoal (3·25 g. and 2 g.), and the resulting yellow solution was diluted (to 1800 c.c.) but no precipitate was obtained until after neutralisation with ammonia, whereupon a pale yellow product (10·72 g.) was obtained, having $[\alpha]_D^{22\cdot5}$ −69° in N-hydrochloric acid.

Part of the product (3 g.) was crystallised thrice (average recovery, 68%) from hot 0·1N-hydrochloric acid, affording a micro-crystalline solid, $[\alpha]_D^{19}$ −47° in N-hydrochloric acid. Better purification was achieved by recrystallising the remainder (6·4 g.) from 20% aqueous acetic acid, two recrystallisations affording a product with $[\alpha]_D^{20}$ −43·4° in N-hydrochloric acid. After five further recrystallisations (average recovery, 78%), the pale yellow product had $[\alpha]_D^{18}$ −22°, unaltered by the last recrystallisation (Found, on material dried at 140° in a vacuum: C, 44·4; H, 5·1. Calc. for $C_{10}H_{13}O_4N_5$: C, 44·9; H, 4·9%).

The foregoing analysed material (148 mg.) was dissolved in 0·1N-sodium hydroxide solution (12 c.c.) and oxidised with excess of potassium permanganate on the water-bath, 5 minutes being allowed after a stable permanganate colour was attained. The product, isolated in the usual way, was dissolved in dilute sodium hydroxide solution (*ca.* 17 c.c.) and 1·5 volumes of filtered 50% sodium hydroxide solution were added. The solid (109 mg.) which separated on cooling was collected after standing for 36 hours in the ice-chest, and the colourless mother-liquors remained clear on acidification with acetic acid. The solid was recrystallised from 2N-sodium hydroxide, affording a crop (*A*) (57·6 mg.) and mother-liquors (*B*). The material (*A*) showed a turquoise-blue fluorescence in aqueous solution, and further recrystallisation of this product from 2N-sodium hydroxide (8 c.c.) afforded the sodium salt (47·7 mg.) of 2-amino-4-hydroxypteridine-7-carboxylic acid (VIII), exhibiting its characteristic bright green fluorescence in aqueous solution and distinctive absorption spectrum. The free acid was analysed (Found, on material dried at 160° in a vacuum: C, 40·7; H, 3·1. Calc. for $C_7H_5O_3N_5$: C, 40·6; H, 2·4%).

The mother-liquors (*B*) were acidified with acetic acid and the precipitate (34·2 mg. was collected

(Found, on material dried at 160° in a vacuum: C, 38·8; H, 2·2. Calc. for $C_7H_5O_2N_5$: C, 40·6; H, 2·4%). Despite the poor value for carbon, this substance showed properties identical with those of 2-amino-4-hydroxypteridine-6-carboxylic acid (IX); the sodium salt showed the typical intense sky-blue fluorescence in aqueous solution and the ultra-violet absorption spectrum in alkaline solution agreed in every detail with that of the authentic substance.

Effect of Hydrazine on the Condensation of p-*Tolyl*-D-*isoglucosamine with* 2 : 4 : 5-*Triamino-6-hydroxypyrimidine. Formation of* 2-*Amino*-4-*hydroxy*-6-D-*arabotetrahydroxybutylpteridine* (II).—A mixture of *p*-tolyl-D-*iso*glucosamine (13·15 g.), 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate (14 g.), sodium acetate trihydrate (15 g.), boric acid (6 g.), and hydrazine hydrate (4 c.c.; 90%) in water (140 c.c.) was heated on the water-bath in a slow stream of nitrogen for 6 hours. The clear brown solution deposited a reddish-brown solid (6·94 g.), which was collected, washed, and dried. The entire crude product was dissolved in N-hydrochloric acid (100 c.c.), and the solution was treated twice with charcoal (2·5 g. and 3 g.), diluted to 0·1N., and neutralised with ammonia, affording a pale yellow product (4·66 g.), $[\alpha]_D^{22}$ −83° in N-hydrochloric acid; this specific rotation was unaltered when the substance (2 g.) was recrystallised from 20% acetic acid (recovery, 73%) (Found, on material dried at 140° in a vacuum: C, 42·7; H, 5·1. Calc. for $C_{10}H_{13}O_6N_5$: C, 42·4; H, 4·6%).

The observed specific rotation is in good agreement with our previously observed values, −81·5° and −86·6°, for the same substance prepared from glucose and fructose respectively. Oxidation with potassium permanganate in the usual way afforded 2-amino-4-hydroxypteridine-6-carboxylic acid (IX), identified by the sky-blue fluorescence of its sodium salt in aqueous solution and by the maximum in its absorption spectrum in 0·1N-sodium hydroxide at 261—262 mμ.; the product of this condensation was therefore 2-amino-4-hydroxy-6-D-*arabo*tetrahydroxybutylpteridine (II).

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447. *Dipole Moment and Spectrographic Data for Certain Diazophenols and Diazonaphthols.*

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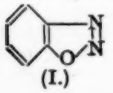
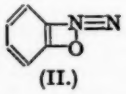
The dipole moments and ultra-violet spectra of two diazophenols and four diazonaphthols indicate that quinonoid structures contribute predominantly to the real structures, in contrast with benzthiadiazole, for which a covalent cyclic formulation seems satisfactory. Data for " azibenzil " are also included.

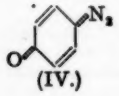
RECENTLY (*Chem. and Ind.*, 1948, 158, 543, 732, 782) reasons were listed for believing that, in certain molecules containing it, the azo-grouping is able to adopt a *cis*-configuration. Similarities between *cis*-azobenzene and benzocinnoline (Calderbank and Le Fèvre, *J.*, 1948, 1949) formed part of the evidence, since in the latter molecule a *cis*-arrangement is fixed by ring formation. Other substances possibly having the same structural feature became, therefore, of obvious relevance, and we accordingly investigated representative members of the classes covered by the title of this paper.

History.—Satisfactory formulations for these compounds have been debated for years. Since they were theoretically derivable from *o*- and *p*- (but not *m*-)amino-phenols or -naphthols containing a similar grouping, earlier investigators assumed *ortho*- or *para*-rings to be involved, *e.g.*, (I) (Bamberger, *Ber.*, 1895, **28**, 837; Morgan and Porter, *J.*, 1915, **107**, 645) or (II) (Klemenc, *Ber.*, 1914, **47**, 1407), although Wolff (*Annalen*, 1900, **312**, 119) had favoured quinonoid repre-


(I.)

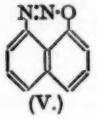

(II.)

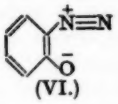
(III.)

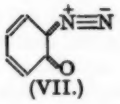

(IV.)

sentations, *e.g.*, (III) or (IV), largely on the argument of colour. Such formulæ have lately received further support from ultra-violet spectroscopy (Anderson and Roedel, *J. Amer. Chem. Soc.*, 1945, **67**, 955). The similarities of properties and reactions—indicating a corresponding similarity of structure—between the *ortho*- and the *para*-series, coupled with the stereochemical awkwardness of a 1 : 4-covalent bridge in the latter, strongly suggest that (I) may be disregarded. The position would be different were the *peri*-diazo-oxide (V)—for which a quinonoid skeleton is impossible—known certainly to exist. It has been mentioned in a number of German patents

(cf. Morgan and Micklethwait, *J.*, 1908, **93**, 607), but Anderson and Roedel (*loc. cit.*) specifically report their unsuccessful attempts to repeat its preparation.


(V.)


(VI.)


(VII.)

Hodgson and Marsden (*J. Soc. Dyers Col.*, 1943, **59**, 271) concluded that all known diazo-oxides can be best regarded as resonance hydrids, *e.g.*, (VI) ⟷ (VII), or generally :—

(VIII.) $\bar{O}—C_6H_4—\overset{+}{N}\equiv N \longleftrightarrow O=C_6H_4=\overset{+}{N}=\bar{N}$ (IX.)

Present Work.—The last suggestion is amenable to examination by means of dipole moments. If this hypothesis were correct, it is obvious that observed polarities should considerably exceed the values expected for the fully quinonoid structures such as (VII) or (IX) in proportion as the ionised forms contribute to the real structures. Wyman (*Chem. Reviews*, 1936, **19**, 213) has noted that true " zwitterion " molecules probably have the large moments which their formulæ indicate.

For the present enquiry, therefore, we made the necessary measurements on the substances listed in Table I. In the third and the fourth column we list estimated moments (μ_Q and μ_Z) for the quinonoid and ionised molecules, respectively. These values are necessarily somewhat speculative. Ordinary benzenoid geometry, atomic radii, etc., have been assumed, together with $\mu_{C:O}$ = *ca.* 3 D. (cf. acenaphthaquinone or phenanthraquinone, Caldwell and Le Fèvre, *J.*, 1939, 1614), $\mu_{C:N_2}$ = *ca.* 1·4 D. (cf. the diaryldiazomethanes, Sidgwick, Sutton, and Thomas, *J.*, 1933, 406), $\mu_{C\cdot NO_2}$ = 4 D., and $\mu_{C\cdot Br}$ = 1·5 D. (cf. the corresponding $C_6H_5{\cdot}X$ compounds). In the fifth column are shown the solutions to the equation, $\mu_{observed} = \alpha_Q^2\mu_Q + \alpha_Z^2\mu_Z$ (cf. Sutton, *Trans. Faraday Soc.*, 1934, **30**, 789), where α_Q^2 and α_Z^2 indicate the relative importances of the contributing forms.

TABLE I.

	$\mu_{obs.}$	μ_Q.	μ_Z.	α_Q^2.	α_Z^2.
3 : 5-Dibromo-1 : 2-benzoquinone-2-diazide	2·9	2·5	13·1	1	0
1 : 2-Naphthaquinone-1-diazide	4·0	3·9	13·7	1	0
1 : 2-Naphthaquinone-2-diazide	3·5	3·9	13·7	1	0
4-Nitro-1 : 2-naphthaquinone-1-diazide	4·6	2·8	16·2	0·9	0·1
1 : 4-Naphthaquinonediazide	4·2	1·6	27·4	0·9	0·1
p-Benzoquinonediazide	5·0	1·6	27·4	0·9	0·1

From the data in Table I it appears that contributions from fully dipolar structures are small. A preliminary forecast of this conclusion has already appeared (Anderson and Le Fèvre, *Nature*, 1948, **162**, 449).

In this connection we note the evidence from studies of thermal decomposition (Vaughan and Phillips, *J.*, 1947, 1560), where certain *o*-diazo-oxides appear to be less stable than their *p*-analogues. The differences are explained by a restriction of resonance in the former by the proximity of opposite electrostatic charges, the ionised form thus tending to preponderate, and the resonance energy to have a smaller value, so causing a lessening of stability. At first sight our results seem to indicate, if anything, a situation which contradicts this prediction.

Recognising, however, the uncertainty of the assumptions we have made, we hesitate to conclude from the six examples in Table I that contributions from fully dipolar forms are more marked in the *p*- than in the *o*-series, since we have also found that the parent substance (III) can be isolated only as a hydrate, which has not yet been successfully dehydrated. We have examined (III) spectroscopically in alcoholic solution, but it has proved too sparingly soluble in benzene for measurement of the dielectric constant. It therefore possibly has a high polarity, and would in this way support the theory of Vaughan and Phillips.

While disregarding a formula of type (I) for the *o*-series, we are not unaware that moments of the orders now found, *e.g.*, for the dibromo-derivative, might be expected on its basis. However, in addition to the reason already given (chemical resemblances between 1 : 2- and 1 : 4-members), we may add another, namely, that O- and S-containing heterocyclic analogues usually have a recognisable parallelism in physical properties such as m. p., b. p., colour, solubility, etc. We have accordingly examined benz-1-thia-2 : 3-diazole (I; S substituted for O) which, in contrast to all the substances of Table I, is low-melting, colourless, easily soluble in non-polar solvents, and volatile in steam (*vide* Beilstein, " Handbuch," **27**, 567).

Yet, notwithstanding the complete dissimilarity from the diazo-oxides, its dipole moment (3·5$_4$ D.) is of their order, and of that to be expected from rough vectorial considerations (cf. Hunter and Partington, *J.*, 1933, 87, *re* $\mu_{O\text{-}S}$). Hodgson and Marsden (*loc. cit.*) commented on the significance of the apparent non-existence of *p*-diazo-sulphides and drew the conclusions, with which we agree, that the 1 : 2-sulphides, unlike the oxides, possess a covalent $-N{=}N-X-$ chain. Such a decision is not novel (cf. Sidgwick, " Organic Chemistry of Nitrogen," Oxford, 1937, p. 422, where incidentally the related triazoles are included with the thiadiazoles). Its interest to us (*vide Chem. and Ind.*, 1948, 158) lies in the fact that, with benzcinnoline, here is another quite stable molecule *in which the* $-N{=}N-$ *arrangement is* cis-.

Absorption Spectra.—Various new determinations have been made, using the Beckman photoelectric spectrophotometer, model D.U. They are incorporated with previously recorded data in Tables II, III, and IV. The three groupings used in the above tables are chosen somewhat arbitrarily to show the degree of resemblance between the absorption by related molecules containing $>C{=}N_2$ and $>C{=}O$. Such a parallelism was first claimed by Wolf (*Z. physikal. Chem.*, 1932, *B*, **17**, 46) for ethyl diazoacetate and certain ketones, although Hantzsch and Lifschitz (*Ber.*, 1912, **45**, 3011) had previously used it to decide that *p*-diazophenol was quinonoid in character. Its most extensive application to the present problem has been by Anderson and Roedel (*loc. cit.*). The measurements made with our various products obtained in attempted preparations of the unsubstituted 1 : 2-benzoquinonediazide (III) are not included in Table III since they were qualitative only. Absorptions were noted as follows :

(*a*) Ethereal extract from alkaline solution	422	300	272	256	242
(*b*) Ethereal extract from acid solution	416	308	272	255 *	—
(*c*) Alcoholic solution of solid after partial dehydration to constant weight	403	—	—	263	—

* Inflexion.

A certain similarity with the results of Table II is apparent. Fukushima and Horio (*Mem. Coll. Eng. Kyoto Imp. Univ.*, 1931, **6**, 179) have likewise reported semiquantitative spectra for the diazotisation products of *o*-, *m*-, and *p*-aminophenol and 1-amino-2-naphthol-4-sulphonic acid. Their figures for maximum absorption are :

Product from *o*-aminophenol	392; 345 *; 263.
,, ,, *p*-aminophenol	358 *; 338; 238; 212.*
,, ,, aminonaphtholsulphonic acid	393; 327; 286; 247.*

TABLE II.

Diazides.

p-Benzoquinonediazide	*E* [1]	448 * (1·80)	342 (4·47)	287 (3·37)
				279 (3·51)
				269 (3·53)
1 : 4-Naphthaquinonediazide	*E* [1]	477 * (1·81)	371 (4·55)	312 (3·83)
			354 (4·38)	291 (4·00)
				282 (4·00)
				242 (3·73)
3 : 5-Dibromo-1 : 2-benzoquinonediazide	*H* [5]	—	419 * (3·55)	285 (3·97)
			408 (3·59)	275 * (3·92)
			349 * (3·31)	226 (4·14)
4-Nitro-1 : 2-benzoquinone-1-diazide	*A* [5]	—	396 (3·79)	258 (4·07)
			325 (4·03)	238 (4·00)
1 : 2-Naphthaquinone-1-diazide	*E* [1]	455 * (2·1)	404 (3·65)	285 (4·21)
			388 (3·78)	278 * (4·13)
			370 (3·72)	250 (4·29)
			335 (3·43)	
			322 (3·42)	
1 : 2-Naphthaquinone-2-diazide	*E* [1]	475 * (2·0)	413 * (3·82)	305 (3·80)
			397 (4·00)	293 (3·80)
			389 * (3·95)	261 (4·57)
			372 * (3·82)	
			317 (3·70)	
4-Nitro-1 : 2-naphthaquinone-1-diazide	*H* [5]	—	400 * (3·49)	284 (3·90)
			395 (3·51)	247 (4·16)
			332 (3·35)	225 (4·26)
Azibenzil	*E* [1,5]	434 (2·04)	319 (3·73)	264 (4·29)

Inflexions are indicated by asterisks, and solvents by *A* = alcohol, *E* = ether, *H* = *n*-hexane in this and other tables.

TABLE III.

Related quinones and benzil.

p-Benzoquinone	*H* [3,4]	478 (1·08) 457 (1·29) 434 (1·30)	—	280 (2·57) 242 (4·34)
,,	*E* [4]	472 (1·10) 455 (1·28) 443 (1·18) 429 (1·30) 417* (1·13) 412 (1·20)	—	278 (2·85) 242 (4·36)
,,	*A* [4]	435 (1·28)	—	296 (2·63) 242 (4·25)
1 : 2-Naphthaquinone	*E* [1]	538 (1·55) 503 (1·54)	389 (3·55) 331 (3·54)	252 (4·52) 248 (4·50)
1 : 4- ,,	*E* [1]	424 (1·65) 403 (1·67)	331 (3·50)	below 250
Benzil	*E* [1]	386 (1·83) 368 (1·81)	335 * (2·22)	273 * (4·1) 259 (4·36)

TABLE IV.

Thiadiazoles and triazoles.

Benz-1-thia-2 : 3-diazole	*H* [5]	—	306 (3·63)	264 (3·92) 254 (4·02) 225 (4·23)
Naphtho(1′ : 2′-5 : 4)-1 : 2 : 3-thiadiazole	*E* [1]	—	353 (3·35) 338 (3·37)	282 * (3·93) 255 (4·76)
Benz-1 : 2 : 3-triazole	*A* [2]	—	291 * (3·32)	282·5* (3·58) 276 (3·65) 259 (3·58)
Naphtho(1′ : 2′-5 : 4)-1 : 2 : 3-triazole	*E* [1]	ca. 350 * (1·70)	342 (3·81) 316 * (3·42) 312 (3·68) 305 (3·35) 298 (3·37)	283 (4·06) 272 (4·07) 251 (4·57) 247 (4·60)

[1] Anderson and Roedel (*loc. cit.*).
[2] Klingstedt, *Compt. rend.*, 1923, **176**, 1550.
[3] Macbeth and Price, *J.*, 1936, 111.
[4] Braude, *J.*, 1945, 490.
[5] Present work.

They remark on the difference between the data just quoted and those for the product from *m*-aminophenol (compare the non-occurrence of 1 : 3-diazo-oxides).

A propos formula (VI) it is relevant that the spectra of Table II are quite distinct from those of corresponding methoxy-diazonium salts, for which Wohl (*Bull. Soc. chim.*, 1939, **6**, 1319) has found :

o-Sulphate ..... 353 (3·65); 263 (4·05).
p- ,, ... 326 (4·10); 311 (4·50); 291 * (4·00); 270 * (3·55); 254 (3·05).

Finally, Tables II and IV, in conjunction, again suggest separate structures for the diazo-oxides and the thiadiazoles, and similar ones for the latter and the triazoles. When S replaces O or NH, the change is generally indicated spectrometrically more by alterations of intensity than of wave-length of maximum absorption. A few examples are collected in Table V. The appearance of extra bands is sometimes notable :

TABLE V.

Oxygen compounds.		Sulphur compounds.		Nitrogen compounds	
Et·O·Et [1]	190 * (3·00)	Et·S·Et [1]	195 (3·15)	Et·NH·Et [1]	195 (3·45)
Ph·OH [1]	275 f. (2·30)	Ph·SH [1]	269 f. (2·86)	Ph·NH_2 [1]	280 f. (2·30)
Furan [1,2]	250 (0·00) 200 * (4·00)	Thiophen [1,2,3]	268 * (−0·25) 241 * (3·22) 234 (3·64) 215 (2·1)	Pyrrole [1,2]	240 (2·48) 210 (4·18)
Oxazole [4]	230 (1·48)	Thiazole [1]	240 (3·60)	Glyoxaline [1]	250 (1·78.)

[1] Braude, *Ann. Reports*, 1945, **42**, 105.
[2] Godart, *J. Chem. Phys.*, 1937, **34**, 70.
[3] Menszel, Thesis, Zurich, quoted in (2).
[4] Cornforth and Cornforth, *J.*, 1947, 96.
f. indicates a group of subsidiary maxima.

By analogy, therefore, if the diazo-oxides were structurally related to the thiadiazoles they should not absorb at wave-lengths much greater than 350 mμ. In fact, of course, their absorption extends right up to the visible region. By the reverse argument, noting that thioketones often absorb in the red (Braude, *loc. cit.*), the transparency of the thiadiazoles down to 350 mμ. strongly suggests that, in them, the C=S group is absent.

Experimental.

Materials.—3 : 5-Dibromo-1 : 2-benzoquinone-2-diazide was prepared (yield, 12%) as stated by Orton (*Proc. Roy. Soc.*, 1903, **71**, 153). It decomposed at 140° after preliminary melting at temperatures which varied with the rate of heating; Orton (*loc. cit.*) and Bamberger and Kraus (*Ber.*, 1906, **39**, 4251) record the same phenomenon.

The isolation of *o*-benzoquinonediazide was attempted many times. Spectroscopic indications were that it was formed during the diazotisation of *o*-aminophenol, *e.g.*, addition of ether immediately after the sodium nitrite, followed—under vigorous stirring—by aqueous sodium hydroxide during 15 minutes until the whole was alkaline, gave, after drying (Na_2SO_4), the solution whose absorptions have already been mentioned (*a*, p. 2084); further acidification of the aqueous portion with nitric acid and another extraction with ether, etc. afforded the second solution (*b*, p. 2084).

A solid was finally obtained by diazotising, at 5° with amyl nitrite (7 c.c.), *o*-aminophenol (5 g.) in alcohol (80 c.c.) containing hydrogen chloride (5 g.). The diazonium chloride was isolated by precipitation with ether, suspended in amyl alcohol (100 c.c.), and stirred at 0° with moist silver oxide in the dark for 2 hours. The mixture was then filtered, the filtrate cooled with alcohol–carbon dioxide, and the product precipitated by ether (*ca.* 800 c.c.). In this way, bright yellow crystals, appearing pale yellow after filtration and washing with ether, were obtained, having m. p. 66° (decomp.). The material was sparingly soluble in carbon tetrachloride, benzene, dioxan, ether, ethyl acetate, or chloroform, easily soluble in methyl, ethyl, or amyl alcohol, and very soluble in water. Its solutions were pale yellow to yellow depending on the solubility. It coupled readily with aqueous alkaline β-naphthol. The absorption in water is noted (*c*, p. 2084). The solid seemed to be a polyhydrate. It did not give reproducible analyses. Over sulphuric acid it slowly lost weight to a constant value, but the final preparation still contained water and exhibited the solubility behaviour just mentioned.

Anderson and Roedel (*J. Amer. Chem. Soc.*, 1945, **67**, 955) obtained *p*-benzoquinonediazide by digesting an absolute alcoholic solution of *p*-hydroxybenzenediazonium chloride with silver oxide, filtering, and removing the solvent with dry air at 0°. We obtained it more conveniently (12% yield) by cooling the alcoholic filtrate to −30° (alcohol–solid carbon dioxide). Its properties agreed with those given by Hantzsch and Davidson (*Ber.*, 1896, **29**, 530) and Anderson and Roedel (*loc. cit.*).

Regarding 1 : 2-naphthaquinone-1-diazide and its 1 : 4-isomer, the directions of Anderson and Roedel were followed, except that it proved advantageous to separate the intermediate diazonium hydrogen sulphates instead of the chlorides. In the case of the 1 : 4-compound it is then unnecessary to convert the salt into the nitrate before extraction. The m. p.s observed were 94—95° and 123°, and yields obtained were 43% and 19%, respectively. 1 : 2-Naphthaquinone-2-diazide (yield 50%; cf. Orton, *Chem. News*, 1903, **87**, 20) had m. p. 75—76·5°, although Orton as well as Anderson and Roedel quote 77°.

4-Nitro-1 : 2-naphthaquinone-1-diazide (Morgan and Evans, *J.*, 1919, **115**, 1126) decomposed with frothing at 130°. Morgan and Evans give 130—134° "with intumescence." Our yield was 51%. 4-Nitro-1 : 2-benzoquinone-2-diazide (yield, 45%; Griess, *Annalen*, 1860, **113**, 212) exploded sharply at 127°. Noelting and Steimle (*Bull. Soc. chim.*, 1915, [iv], **17**, 392) mention explosion at 118°, whilst Griess notes violent explosability at 100°.

The above substances were all recrystallised from the solvents prescribed by the authors cited.

Benz-1-thia-2 : 3-diazole.—2 : 2′-Dinitrodiphenyl disulphide (Blanksma, *Rec. Trav. chim.*, 1901, **20**, 127; 7 g.) was reduced by tin and hydrochloric acid, etc., as described by Claasz (*Ber.*, 1912, **45**, 1029). After precipitation of the tin by hydrogen sulphide, filtration, and concentration to one-fifth volume, cooling to 5°, and diazotisation ($NaNO_2$; 5 g.), the mixture was steam-distilled. The total condensate was extracted with ether, and the product (yield calc. on disulphide, 50%) recovered by evaporation. Its m. p. was 35° in agreement with that given by Jacobson (cf. Beilstein, "Handbuch," XXVII, 568, for references).

Dipole Moment Estimations.—For these, apparatus and methods already described (cf. Calderbank and Le Fèvre, *J.*, 1948, 1949) have been utilised, benzene being the solvent throughout. The symbols used in Tables VI—VIII have been defined in many previous papers (or see "Dipole Moments," 2nd Edn., Methuen, 1948, pp. 39—42).

Because of their relevance the following unpublished data for "azibenzil," $CPh(N_2)\cdot COPh$, are added. They were obtained in collaboration with Mr. C. C. Caldwell at University College, London, 1939, a Pulfrich refractometer being used, with a divided cell, and other components as in "Dipole Moments," 2nd Edn., Methuen, 1948, Ch. II.

$10^6 \times w_1$.	ε_{25}.	d_4^{25}.	p_{13}.	P_1.	n_D^{25}.	r_{13}.	$[R_L]_D$.
0	2·2725	0·87378	0·34086	—	1·49360	0·33294	—
5,150	2·2937	0·87498	0·34425	226·1	—	—	—
9,170	2·3106	0·87601	0·34708	226·2	1·49471	0·33270	68·1
14,050	2·3312	0·87720	0·35038	226·0	1·49530	0·33262	68·9
18,020	2·3479	0·87818	0·35301	225·3	1·49577	0·33251	68·6
26,480	2·3839	0·88022	0·35863	224·6	1·49677	0·33231	68·6

Molecular Refractions.—Owing to conjugation a quinonoid form such as (III) should, compared with its cyclic isomeride, *e.g.*, (I), show marked exaltation of molecular refraction. No data are on record

TABLE VI.

Dielectric-polarisation Measurements.

$10^6 \times w_1$.	ε_{25}.	d_4^{25}.	$\alpha\varepsilon_2$.	βd_2.
0	2·2725	0·87378	—	—
3 : 5-Dibromo-1 : 2-benzoquinone-2-diazide.				
4,325	2·2884	0·87600	3·68	0·513
7,850	2·3025	0·87790	3·82	0·525
10,161	2·3125	0·87912	3·94	0·526
12,563	2·3221	0·88050	3·95	0·535
14,556	2·3303	0·88158	3·97	0·522
1 : 2-Naphthaquinone-1-diazide.				
2,425	2·3005	0·87442	11·56	0·264
2,949	2·3068	0·87454	11·64	0·258
4,899	2·3256	0·87519	10·84	0·288
7,283	2,3470	0·87574	10·23	0·269
1 : 2-Naphthaquinone-2-diazide.				
3,707	2·3041	0·87481	8·52	0·278
4,339	2·3098	0·87500	8·60	0·281
6,654	2·3304	0·87567	8·70	0·284
4-Nitro-1 : 2-naphthaquinone-1-diazide.				
1,586	2·2902	0·87436	11·16	0·366
1,664	2·2917	0·87435	11·54	0·343
2,709	2·3033	0·87476	11·37	0·362
2,723	2·3034	0·87472	11·35	0·345
1 : 4-Naphthaquinonediazide.				
2,505	2·3026	0·87445	12·02	0·268
2,849	2·3069	—	12·07	—
3,670	2·3165	0·87488	11·99	0·300
4,092	2·3222	0·87503	12·15	0·306
***p*-Benzoquinonediazide.**				
2,193	2·3251	0·87450	23·98	0·328
2,555	2·3325	0·87464	23·48	0·337
3,438	2·3555	0·87481	24·14	0·300
Benz-1-thia-2 : 3-diazole.				
2,846	2·3022	0·87465	10·45	0·306
5,484	2·3300	0·87541	10·48	0·297
5,988	2·3350	0·87559	10·44	0·302
6,716	2·3429	0·87583	10·49	0·305

TABLE VII.

Refraction measurements.

$10^6 \times w_1$.	$n_D^{25\cdot3}$.	$d_4^{25\cdot3}$.	r_{12}, c.c.	$[R_L]_D$, c.c.
0	1·4964	0·87350	0·33465	—
3 : 5-Dibromo-1 : 2-benzoquinone-2-diazide.				
11,550	1·4988	0·87985	0·33360	67·7
$10^6 \times w_1$.	n_D^{25}.	d_4^{25}.	r_{12}, c.c.	$[R_L]_D$, c.c.
0	1·4980	0·87378	0·33546	—
1 : 2-Naphthaquinone-1-diazide.				
16,030	1·5010	0·87833	0·33543	56·7
1 : 2-Naphthaquinone-2-diazide.				
10,050	1·5000	0·87675	0·33546	57·1
4-Nitro-1 : 2-naphthaquinone-1-diazide.				
10,970	1·4998	0·87764	0·33501	63·3
1 : 4-Naphthaquinonediazide.				
3,409	1·4990	0·87483	0·33563	65·5
Benz-1-thia-2 : 3-diazole.				
18,910	1·5003	0·87957	0·33456	39·2

TABLE VIII.

Calculation of results.

	M.	Mean $\alpha\varepsilon_2$.	Mean β.	$_\infty P_1$, c.c.	$[R_L]_D$, c.c.	μ, D.
3 : 5-Dibromo-1 : 2-benzoquinone-2-diazide	227·9	3·87	0·600	240·1	67·7	$2\cdot8_9$
1 : 2-Naphthaquinone-1-diazide	170·2	11·07	0·308	394·4	56·7	$4\cdot0_4$
1 : 2-Naphthaquinone-2-diazide	170·2	8·61	0·322	314·9	57·1	$3\cdot5_3$
4-Nitro-1 : 2-naphthaquinone-1-diazide	215·2	11·37	0·405	503·7	63·3	$4\cdot6_3$
1 : 4-Naphthaquinonediazide	170·2	12·06	0·332	424·7	65·5	$4\cdot1_7$
p-Benzoquinonediazide	$120\cdot0_5$	23·87	0·368	564·7	(52) *	$4\cdot9_3$
Benz-1-thia-2 : 3-diazole	136·2	10·46	0·346	298·3	39·2	$3\cdot5_4$
"Azibenzil"	222·1	4·18	0·278	229·3	68·7	$2\cdot7_9$

* Estimated from the refraction of the dibromo-derivative.

for *o*-benzoquinone, but for *p*-benzoquinone the $(R_L)_D$ observed in benzene solution exceeds the calculated value by *ca.* 4 units (Le Fèvre and Le Fèvre, *J.*, 1935, 1696); for phenanthraquinone the corresponding quantity is 5 units.

The measured $[R_L]_D$ for benzthiadiazole is 39—40 c.c. (Table VIII). To check this, the refractivity of the –N=N– system is required. According to Auwers and Heimke (*Ber.*, 1928, **61**, 1030) this is *ca.* 3·2 c.c. for a non-conjugated azo-group. However, later studies in quinoline or α-methylnaphthalene solutions (Auwers, *Ber.*, 1938, **71**, 611) have shown *cis*-azobenzene to have $[R_L]_D = 59·3$; since $C_6H_6 = 26·1$ and H = 1·1, the *cis*-azo-configuration must be equivalent to 9·3 c.c. Taking these figures, we calculate for benzthiadiazole $[R_L]_D = 23·9 + 9·3 + 7·8$ (for bivalent sulphur) = 41·0. This is of the order found. On the other hand, a parallel calculation for formula (I), in which O = 1·6 (*i.e.*, "ether" oxygen) is used, leads to $[R_L]_D = 34·8$, which minus 2·2 (2 × H) plus 17·8 (2 × Br) = 50·4 c.c. Yet the value we record for 3 : 5-dibromo-1 : 2-benzoquinone-2-diazide is 67·7 c.c.—an apparent exaltation of 17·3 c.c. The naphthaquinonediazides of Table VII similarly show exaltations of 10—20 c.c. These are surprisingly large estimates, reminiscent of Smedley's measurements on diphenylbutadiene and diphenylhexatriene (exaltations of 15 and 24, respectively; *J.*, 1908, **93**, 376). The refractivity appropriate to an "$-N_2-$" group is evidently sensitively dependent upon environment. Thus in azibenzil ($[R_L]_D = 68·7$, present work), $-N_2-$ appears as 68·7 − 50 (2 × C_6H_5) − 4·84 (2 × C) − 2·21 (ketonic oxygen) = 11·7, in ethyl diazoacetate as 28·7 − [22·2$_5$(for $CH_2{\cdot}CO_2Et$) − 2·2 (2 × H)] = 8·7 (Wolf, *Physikal. Z.*, 1930, **31**, 227; Brühl, *Z. physikal. Chem.*, 1895, **16**, 214) and in di-*p*-chlorophenyldiazomethane as 81 − (62·2 − 2·2) − 2·4 = 18·6 c.c. ($C_6H_5Cl = 31·1$, and the diazo-compound = 81 for light of λ 5790; Sidgwick, Sutton, and Thomas, *loc. cit.*; unreferenced *R* data are from Landolt-Börnstein's "Tables").

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448. *The Thermotropy of Certain Benzonaphtho- and Dinaphtho-bisspiro-2-pyrans in Benzene Solutions.*

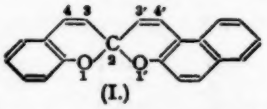
By A. A. HUKINS and R. J. W. LE FÈVRE.

Of the various explanations in the literature for the reversible colour changes shown by a number of *spiro*pyrans when successively heated and cooled, only those involving the production of, or increasing contributions to a mesomeride from, fully ionic forms seemed to accord with all recorded observations.

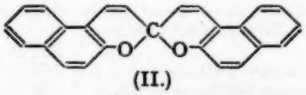
Such explanations may, however, be incorrect, since it is now found that the development of colour is not accompanied by any noticeable increase of dipole moment. Present measurements do not entirely eliminate possibilities that the thermally generated chromogens are of *o*-quinonoid type.

SENIER AND SHEPHEARD, in a series of papers (*J.*, 1909—1912), obviously thought there was some connection between phototropy and thermotropy (cf. *J.*, 1909, **95**, 1943). Having previously (de Gaouck and Le Fèvre, *J.*, 1939, 1457) found that certain strongly phototropic crystalline anils ceased to be phototropic on dissolution, we thought it of interest to investigate a number of *spiro*pyrans which have been reported to exhibit *thermotropy in the dissolved condition.*

These substances are derivatives of benzonaphtho- and dinaphtho-bis*spiro*-2-pyrans (I and II) (Löwenbein and Katz, *Ber.*, 1926, **59**, 1377; Dilthey, Berres, Hölterhoff, and Wübken, *J. pr. Chem.*, 1926, **114**, 179; Dickinson and Heilbron, *J.*, 1927, 14, 1699; Heilbron and Irving, *J.*, 1933, 430), which, in *cold* solvents, form colourless solutions assuming, as their temperatures are raised, an intense violet-blue colour. The phenomenon, when it occurs, appears to be reversible, and after many repetitions the solutes can be recovered in their original purity. Heilbron *et al.* (*loc. cit.*) at first considered such behaviour to be limited to molecules having (*a*)



(I.)

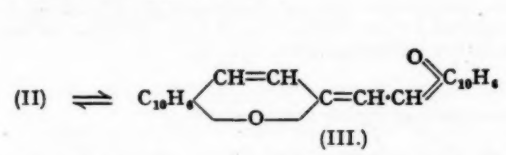


(II.)

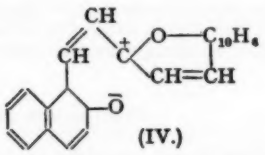
at least one naphthalene nucleus, and (*b*) an unsubstituted 3′-carbon atom in the naphthopyran ring, but they later (1933) demonstrated that it could still occur if the 3 : 3′-positions were bridged by polymethylene chains. Since then, Wizinger and Wenning (*Helv. Chim. Acta*, 1940, **23**, 247) have also reported similar properties for a number of naphthopyrans in which the other component is heterocyclic, *e.g.*, $O(C_6H_4)_2C<$, $MeN(C_6H_4)_2C<$, or $C_6H_4<\begin{matrix}CMe_2\\NMe\end{matrix}>C<$.

In the present work we have prepared di-β-naphtho- and benzo-β-naphtho-bis*spiro*-2-pyran, and the isomeric 3- and 3′-monomethyl derivatives, the last being chosen because it does not become coloured even in hot xylene. Further, Löwenbein and Dilthey have independently shown that the molecular weights of these compounds are normal both in the white and in the purple condition.

Proposed Mechanisms.—Dickinson and Heilbron, and Löwenbein and Katz initially attributed the production of colour to an intramolecular change from the *spiro*- (as I or II) to an *o*-quinonoid type (*e.g.*, III) :



(III.)



(IV.)

Dilthey *et al.* (*loc. cit.*) rejected this hypothesis and suggested ionic dissociation as a cause, the coloured molecule being heteropolar, *e.g.*, as in (IV). Dickinson and Heilbron (*loc. cit.*, p. 1702) then wrote formulæ involving ionised chelates, but later withdrew them in the face of their own further experimental evidence (*loc. cit.*, 1933). The possibilities of free-radical formation have been considered by Heilbron, Löwenbein, and Dilthey, and by each found incompatible with observed chemical reactions, *e.g.*, prolonged oxygen treatment of hot solutions causing no diminution of colour, quinol being without effect, etc. Schönberg and Sina (*J.*, 1947, 175), by implication, regard these *spiro*pyrans as resonance hybrids between the neutral and the ionised structures (*e.g.*, between II and IV).

Present Work.—Explanations involving the intervention of ionised forms would require the development of colour to be accompanied by an increase of polarity. The dipole moment of, *e.g.*, (IV), when fully ionised, is clearly not less than *ca.* 10 D., while the original molecules (*e.g.*, I or II) will, from elementary vectorial principles, have moments lying around $(2\mu^2\cos^2 30°)^{\frac{1}{2}} = 1{\cdot}23\ \mu$ (where μ is the component moment acting roughly through each oxygen; regular hexagonal rings being assumed throughout). The calculation resembles that for 2 : 2′-disubstituted diphenyls (*J.*, 1938, 967) with an azimuthal angle of 90°. Plausible values for μ might be selected between those of coumarone (0·8 D.; Syrkin and Schott-Lvova, *J. Physical Chem. U.S.S.R.*, 1938, **12**, 479) and di-*p*-tolyl ether (1·4 D., Faraday Soc. List, 1934), whence the colourless *spiro*pyrans should show moments in the range 1—1·7 D.

Experimental.

The *spiro*pyrans were prepared as indicated by Dickinson and Heilbron (*loc. cit.*), the m. p.s given by them being added in parentheses: Benzo-β-naphthobis*spiro*-2-pyran, from aqueous acetone, m. p. 167° (168°); 3-methyl-β-, from acetone, m. p. 149° (149°); 3′-methyl-β-, from absolute alcohol, m. p. 176° (177°); di-β-naphthobis*spiro*-2-pyran, from xylene, m. p. 160° (160°).

Measurements tabulated below have been made by means of the apparatus and techniques already reported (*J.*, 1948, 1949). They are set out under customary headings (explained in *J.*, 1937, 1805, wherein our method of calculation is also described). Refractive indices were observed with an Abbé refractometer. The solvent was benzene throughout—a preliminary test showing that it allowed a sufficient temperature range for the 3-methyl compound to develop a strong colour; AnalaR grade material was partly frozen, decanted, dried, and stored over sodium wire. The range of concentrations available was limited by the sparing solubilities of the *spiro*pyrans.

Dielectric constant and density coefficients at 25°.

$100w_1$.	ε_{1000}^{25}.	$a\varepsilon_2$.	d_4^{25}.	βd_2.	$100w_1$.	ε_{1000}^{25}.	$a\varepsilon_2$.	d_4^{25}.	βd_2.
0	2·2725	—	0·87378	—	0	2·2725	—	0·87378	—
Benzo-β-naphthobis*spiro*-2-pyran.					Di-β-naphthobis*spiro*-2-pyran.				
0·3604	2·2769	1·22	0·87474	0·2658	0·34503	2·2766	1	0·87477	0·2869
3-Methylbenzo-β-naphthobis*spiro*-2-pyran.					3′-Methylbenzo-β-naphthobis*spiro*-2-pyran.				
0·93642	2·2832	1·14	0·87625	0·2637	0·3886	2·2774	1·25	0·87484	0·2725
1·2373	2·2853	1·03	0·87710	0·2683	0·8848	2·2828	1·16	0·87612	0·2641

A solution of the last compound ($100w_1 = 0{\cdot}62448$) in benzene (n_D^{25} 1·4971; d_4^{25} as above) had n_D^{25} 1·4978 and d_D^{25} 0·87556. Its specific polarisation was therefore 0·33466 c.c., whence the molecular refraction of the solute was 90 c.c. From standard atomic and bond-refraction data the theoretical value was 91 c.c. This agreement justified the use, for the three other *spiro*pyrans, of $[R_L]_D$ figures calculated from the tables of Roth–Eisenlohr (" Refraktometr. Hilfsbuch," Leipzig, 1911).

Calculation of results.

M_1.	Mean $\alpha\varepsilon_2$.	Mean β.	$_\infty P_1$.	$[R_L]_D$.	μ, D.	M_1.	Mean $\alpha\varepsilon_2$.	Mean β.	$_\infty P_1$.	$[R_L]_D$.	μ, D.
Benzo-β-naphthobis*spiro*-2-pyran.						Di-β-naphthobis*spiro*-2-pyran.					
298·3	1·22	0·304	139·1	86·8	$1\cdot4_2$	348·4	1·19	0·328	157·6	102·1	$1\cdot6_4$
3-Methylbenzo-β-naphthobis*spiro*-2-pyran.						3′-Methylbenzo-β-naphthobis*spiro*-2-pyran.					
312·4	1·09	0·316	136·4	91·4	$1\cdot4_7$	312·4	1·20	0·307	144·4	91·4	1·6

The calculations showed that, at 25°, at which temperature the solutions were all colourless, the solutes had dipole moments of the orders to be expected for structures (I) and (II). Similar readings at higher temperatures were next taken, as shown in the following table.

Polarisation and density measurements at higher temperatures.

Temp., t.	d_4^t.	βd_2.	β.	ε_t.	$\alpha\varepsilon_2$.	P_1.
3-Methylbenzo-β-naphthobis*spiro*-2-pyran.						
Solution (i) : $w_1 = 0{\cdot}006052$.						
30°	0·87008	0·2645	0·3045	2·2693	1·074	138
40	0·85940 *	0·2631	0·3067	2·2498	1·124	142
50	0·848743	0·2649	0·3127	2·2296	1·058	139
60	0·83807	0·2640	0·3156	2·2096	1·025	138
Solution (ii) : $w_1 = 0{\cdot}015291$.						
30	0·87246	0·2605	0·3003	2·2781	1·001	134
35	0·86725 *	0·2686	0·3112	2·2682	1·001	133
40	0·86187	0·2656	0·3096	2·2585	0·010	135
45	0·85665	0·2731	0·3204	2·2486	1·012	134
50	0·85127	0·2700	0·3187	2·2385	1·003	134
60	0·84074	0·2790	0·3335	2·2184	0·9816	133
3′-Methylbenzo-β-naphthobis*spiro*-2-pyran. w_1 0·0062448.						
30	0·87016	0·2697	0·3105	2·2702	1·190	144
35	0·86482 *	0·2687	0·2319	2·2602	1·16 *	143
40	0·85943	0·2597	0·3028	2·2500	1·121	142
45	0·85410 *	0·2604	0·3054	2·2404	1·166	145
50	0·84886	0·2748	0·3244	2·2303	1·121	141
60	0·83815	0·2693	0·3220	2·2108	1·191	148

* Estimated by graphical interpolation.

The densities and dielectric constants recorded above were determined relatively to the standard figures (**) at 25° (Hartshorn and Oliver, *Proc. Roy. Soc.*, 1929, **123**, *A*, 664). We have used the following data for evaluating the coefficients, α and β :

t.	ε_t.	d_4^t.	t.	ε_t.	d_4^t.	t.	ε_t.	d_4^t.
25°	2·2725 **	0·87378 **	40°	2·2430	0·85781	50°	2·2232	0·84714
30	2·2628	0·86848	45	2·2331	0·85247	60	2·2034	0·83647
35	2·2529	0·86314						

Discussion.

The solutions of the 3-methylbenzo-compound began to show distinct colour at 40°. They were a deep violet at 60°. The 3′-isomer, however, remained without tint over the whole temperature range. Yet it will be noted that no change of polarisation accompanies the alteration of colour. The variations between the P_1 values for the thermotropic 3-methyl derivative are not more marked than between the corresponding values for the non-thermotropic 3′-isomer. Such irregularities as do occur are probably due to evaporation of solvent at the higher temperatures. It is relevant to mention that, on a basis of $\mu_{solute} = 1{\cdot}5$ D., a rise of 30° should cause P_1 to decrease about 4 c.c. On the other hand, a solute with $\mu = 10$ D. would require a P_1 of *ca.* 1600 c.c. We conclude, therefore, that our results show the negligible production of such fully ionised forms as (IV).

In the face of the recorded chemical evidence already cited, no convincing explanation for these cases of thermotropy seems to be available. Provisionally, the least unacceptable hypothesis is that indicated by (III) above, since it is possible for such structures to be disposed

so that the C–O–C and the C=O component moments will oppose one another in the molecular resultant.

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, March 28th,* 1949.]

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449. *Hydroxamic Acids. Part II. The Synthesis and Structure of Cyclic Hydroxamic Acids from Pyridine and Quinoline.*

By K. G. CUNNINGHAM, G. T. NEWBOLD, F. S. SPRING, and JAMES STARK.

By the general methods devloped in Part I (*J.*, 1948, 1864), several pyridine and quinoline cyclic hydroxamic acids have been prepared. A study of the ultra-violet absorption spectra of the known pyridine cyclic hydroxamic acids and related derivatives leads to the conclusion that in ethanolic solution the acids are 1-hydroxy-2-keto-1 : 2-dihydropyridines and not 2-hydroxypyridine 1-oxides.

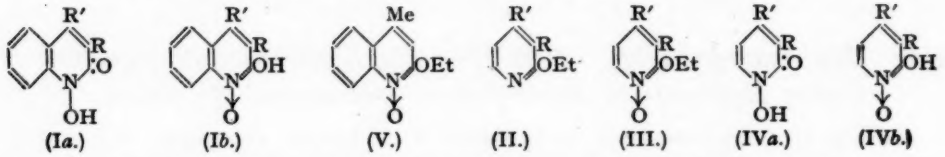
IN Part I of this series Newbold and Spring (*J.*, 1948, 1864) described the preparation of 1-hydroxy-2-keto-1 : 2-dihydropyridine (IV*a*; R = R′ = H) [2-hydroxypyridine 1-oxide (IV*b*; R = R′ = H)] and of 1-hydroxy-2-keto-1 : 2-dihydroquinoline (I*a*; R = R′ = H) [2-hydroxyquinoline 1-oxide (I*b*; R = R′ = H)] by oxidation of 2-ethoxypyridine and of 2-ethoxyquinoline to yield the respective *N*-oxides, followed by acid hydrolysis of the oxides. 1-Hydroxy-2-keto-1 : 2-dihydroquinoline possesses a pronounced *in vitro* inhibitory effect on the growth of *Strep. hæmolyticus*, *Staph. aureus*, and *B. coli*. Subsequent curative tests using mice infected with a mouse-virulent hæmolytic streptococcus, however, showed that death was not delayed by administration of 5 mg. of this compound by oral, intraperitoneal, or subcutaneous routes. The compound was too toxic to allow of the administration of larger doses. The present paper describes the synthesis of a number of related cyclic hydroxamic acids which was undertaken with a view to their antibacterial evaluation.

2-Bromo-3-methylpyridine and *2-bromo-4-methylpyridine* were converted into *2-ethoxy-3-methyl-* (II; R = Me, R′ = H) and *2-ethoxy-4-methyl-pyridine* (II; R = H, R′ = Me), respectively. Treatment of 2-ethoxy-3-methylpyridine with hydrogen peroxide, followed by hydrolysis of the product with dilute mineral acid, gave the hydroxamic acid, *1-hydroxy-2-keto-3-methyl-1 : 2-dihydropyridine* (IV*a*; R = Me, R′ = H), which gives a crystalline copper salt and a positive reaction with ferric chloride. In the case of 2-ethoxy-4-methylpyridine, oxidation with peracetic acid gives *2-ethoxy-4-methylpyridine 1-oxide* (III; R = H, R′ = Me) which immediately liberates iodine from an acidified potassium iodide solution and was characterised by a *picrate*. Hydrolysis of the oxide with mineral acid yields *1-hydroxy-2-keto-4-methyl-1 : 2-dihydropyridine* (IV*a*; R = H, R′ = Me) which shows the characteristic properties of a cyclic hydroxamic acid. Although *2-ethoxy-6-methylpyridine* was successfully oxidised to *2-ethoxy-6-methylpyridine 1-oxide*, characterised as its *picrate*, we were unable to isolate the corresponding cyclic hydroxamic acid from the solution obtained after treatment of the oxide with mineral acid although this gave a deep red colour with ferric chloride.

1-Hydroxy-2-keto-4-methyl-1 : 2-dihydroquinoline (I*a*; R = H, R′ = Me) has been obtained from 4-methylcarbostyril which was converted into 2-ethoxy-4-methylquinoline following the method of Knorr (*Annalen*, 1886, **236**, 102). Oxidation of the last compound with peracetic acid yielded *2-ethoxy-4-methylquinoline 1-oxide*, hydrolysis of which with mineral acid gave the required hydroxamic acid. A different route was employed to synthesise *1-hydroxy-2-keto-3-methyl-1 : 2-dihydroquinoline* (I*a*; R = Me, R′ = H). In this, *ethyl β-o-nitrophenyl-α-methyl acrylate* was reduced with ammonium sulphide to give a mixture from which 3-methylcarbostyril and the required hydroxamic acid were isolated.

In Part I, the simple hydroxamic acid derived from quinoline was described as 2-hydroxyquinoline 1-oxide (I*b*; R = R′ = H) and not as 1-hydroxy-2-keto-1 : 2-dihydroquinoline (I*a*; R = R′ = H). Similarly the cyclic hydroxamic acid derived from pyridine was described as 2-hydroxypyridine 1-oxide (IV*b*; R = R′ = H) and not as 1-hydroxy-2-keto-1 : 2-dihydropyridine (IV*a*; R = R′ = H); comment was made upon the arbitrary nature of this choice. It became of some interest to attempt to differentiate between these two structure-types and, with this in view, a study has been made of the ultra-violet absorption spectra of pyridine cyclic hydroxamic acids and related compounds.

The ultra-violet absorption spectra of various pyridine derivatives are shown in Table I. The unsubstituted pyridine cyclic hydroxamic acid and the corresponding 3- and 4-methyl homologues each show absorption maxima of fairly high intensity at approximately 2300 and 3050 A. This type of absorption spectrum corresponds very closely to that of 2-keto-1 : 2-dihydropyridine and that of 1-methyl-2-keto-1 : 2-dihydropyridine, and is markedly different from that of 2-methoxypyridine and of 2-ethoxy-6-methylpyridine. These results indicate



(Ia.) (Ib.) (V.) (II.) (III.) (IVa.) (IVb.)

that in ethanolic solution the pyridine cyclic hydroxamic acids examined possess the 1-hydroxy-2-keto-1 : 2-dihydro-structure and not the 2-hydroxy 1-oxide structure.

TABLE I.

Ultra-violet Absorption Spectra in Ethanol.

	Max. 1.		Max. 2.	
	A.	ε.	A.	ε.
1-Hydroxy-2-keto-1 : 2-dihydropyridine	2280	6500	3050	4000
1-Hydroxy-2-keto-3-methyl-1 : 2-dihydropyridine	2300	2500	3050	5000
1-Hydroxy-2-keto-4-methyl-1 : 2-dihydropyridine	2300	5000	3030	6700
2-Keto-1 : 2-dihydropyridine [1]	2290	7000	3000	5000
1-Methyl-2-keto-1 : 2-dihydropyridine	2300	6000	3050	5000
2-Methoxypyridine	2700	3500	—	—
2-Ethoxy-6-methylpyridine	2730	6400	—	—

[1] Cf. Specker and Gawrosch, *Ber.*, 1942, **75**, 1338.

The results of antibacterial tests on some of the cyclic hydroxamic acids described in this paper, together with those on some simpler hydroxamic acids, are shown in Table II.

TABLE II.

Minimal Inhibitory Concentration in Mg. per 100 *c.c. of Culture Medium.*

	Strep. haem.		*Staph. aureus.*		*B. coli.*	
	Broth.	Blood.	Broth.	Synthetic.	Broth.	Synthetic.
1-Hydroxy-2-keto-3-methyl-1 : 2-dihydropyridine	0·5	5	2	1	1	1
1-Hydroxy-2-keto-4-methyl-1 : 2-dihydropyridine	2	20	20	10	20	2
1-Hydroxy-2-keto-4-methyl-1 : 2-dihydroquinoline	0·5	>5	5	5	2	1
Glycine hydroxamic acid	20	—	50	—	200	—
DL-Alanine hydroxamic acid	20	—	50	—	200	—
DL-Valine hydroxamic acid	>10	—	>10	—	>10	>10
DL-*iso*Leucine hydroxamic acid	5	—	>50	—	50	—
DL-Phenylalanine hydroxamic acid	20	>20	>20	—	>20	>20
Benzhydroxamic acid	20	—	200	—	200	—
p-Aminobenzhydroxamic acid	10	—	20	—	20	—

In publications which appeared after the manuscript of this paper was completed, Shaw (*J. Amer. Chem. Soc.*, 1949, **71**, 67) and Lott and Shaw (*ibid.*, p. 70) have described the synthesis of 1-hydroxy-2-keto-1 : 2-dihydropyridine and of 1-hydroxy-2-keto-4-methyl-1 : 2-dihydropyridine by essentially the method described by Newbold and Spring (*loc. cit.*); in addition they have obtained the first-named compound in poor yield by the oxidation of 2-pyridone with perbenzoic acid. These authors also describe the ultra-violet spectrum of the unsubstituted pyridine hydroxamic acid and they conclude that it is 1-hydroxy-2-keto-1 : 2-dihydropyridine and not 2-hydroxypyridine-1-oxide.

EXPERIMENTAL.

2-Bromo-3-methylpyridine.—2-Amino-3-methylpyridine (18 g.) was added at 15° to hydrobromic acid (48%; 82·5 c.c.). The solution was cooled to −10° and treated with bromine (25·1 c.c.) added dropwise during 1 hour. A solution of sodium nitrite (28·8 g.) in water (42 c.c.) was added during 2 hours, and the mixture stirred for a further hour. The mixture was treated with a solution of sodium

hydroxide (63 g.) in water (65 c.c.), the temperature being kept below 20°. The solution was extracted with ether, and the extract dried (KOH). After removal of the ether the product was distilled; *2-bromo-3-methylpyridine* was obtained as a colourless oil (22·3 g.), b. p. 81—83·5°/10 mm., n_D^{15} 1·5472 (Found: C, 41·8; H, 3·4. C_6H_6NBr requires C, 41·9; H, 3·5%).

2-Bromo-4-methylpyridine was obtained by the same method starting from 2-amino-4-methylpyridine (yield, 80%). It is a colourless, highly refracting oil, b. p. 87°/10 mm., n_D^{15} 1·5625 (Found: C, 42·0; H, 3·3. C_6H_6NBr requires C, 41·9; H, 3·5%). The *picrate* separates as prisms, m. p. 108°, from ethanol (Found: N, 13·7. $C_{12}H_9O_7N_4Br$ requires N, 14·0%).

2-Ethoxy-3-methylpyridine.—2-Bromo-3-methylpyridine (20·4 g.) was added to a solution of sodium ethoxide in ethanol (from 7 g. of sodium and 140 c.c. of dry ethanol), and the solution heated under reflux for 14 hours. The mixture was concentrated, diluted with water, and extracted with ether. The extract was dried (Na_2SO_4) and distilled. Two main fractions, b. p. 58—63°/9 mm. (9·5 g.) and 70—80°/9 mm. (4·3 g.), were collected. The higher-boiling fraction was 2-bromo-3-methylpyridine. Redistillation of the lower-boiling fraction gave *2-ethoxy-3-methylpyridine* as a colourless oil, b. p. 59—61°/9 mm., n_D^{15} 1·4981 (Found: C, 69·7; H, 7·6. $C_8H_{11}ON$ requires C, 70·1; H, 8·0%). With allowance for recovered starting material, the yield was 59%. The *picrate* separates from ethanol as needles, m. p. 117° (Found: C, 46·5; H, 4·3. $C_{14}H_{14}O_8N_4$ requires C, 45·9; H, 3·8%).

2-Ethoxy-4-methylpyridine was obtained from 2-bromo-4-methylpyridine by the same method, as a colourless oil, b. p. 70°/10 mm., n_D^{16} 1·5005 (yield, with allowance for recovered starting material, 75%) (Found: C, 69·7; H, 7·9. $C_8H_{11}ON$ requires C, 70·1; H, 8·0%). The *picrate* separates from ethanol as leaflets, m. p. 145° (Found: N, 15·1. $C_{14}H_{14}O_8N_4$ requires N, 15·3%).

2-Ethoxy-6-methylpyridine was obtained from 2-bromo-6-methylpyridine (Willink and Wibaut, *Rec. Trav. chim.*, 1934, **53**, 417) in 47% yield by the method described above, as a colourless oil, b. p. 59—60°/10 mm., n_D^{14} 1·4997 (Found: C, 70·5; H, 8·0. $C_8H_{11}ON$ requires C, 70·1; H, 8·0%).

2-Ethoxy-4-methylpyridine 1-Oxide.—An aqueous solution of peracetic acid was prepared by heating equal volumes of hydrogen peroxide (100 vol.) and glacial acetic acid at 90° for 2 hours. The solution was cooled and treated with 2-ethoxy-4-methylpyridine (22 g.), and the mixture maintained at 45° for 24 hours. The solution was evaporated at 25 mm. and finally at 2—5 mm. (bath temp., 40°). The residue was cooled in a freezing mixture and cautiously neutralised with cold 5N-sodium hydroxide. The cold mixture was extracted with chloroform (3 × 50 c.c.), and the dried (Na_2SO_4) extract evaporated under reduced pressure to give an oil which rapidly solidified. The solid (7·0 g.) was collected and recrystallised from dioxan from which *2-ethoxy-4-methylpyridine 1-oxide* separates as hygroscopic needles, m. p. 101—102° (Found: N, 8·4. $C_8H_{11}O_2N,H_2O$ requires N, 8·2%). It immediately liberates iodine in the cold from a solution of potassium iodide acidified with acetic acid. Light absorption in ethanol: Maxima at 2610 A., $\varepsilon = 5300$, and 3040 A., $\varepsilon = 3000$. The *picrate* separates from ethanol as needles, m. p. 139° (Found: C, 44·1; H, 3·9; N, 14·3. $C_{14}H_{14}O_9N_4$ requires C, 44·0; H, 3·7; N, 14·7%).

2-Ethoxy-6-methylpyridine 1-Oxide.—A solution of 2-ethoxy-3-methylpyridine (9·5 g.) in glacial acetic acid (70 c.c.) was treated with hydrogen peroxide (100 vol.; 70 c.c.) and kept at 56° for 19 hours. The solution was concentrated at 30° under reduced pressure, and the residue made alkaline by the addition of 3N-potassium hydroxide at 0°. The solution was extracted with chloroform (6 × 35 c.c.), and the extract dried (Na_2SO_4) and evaporated. The residue was crystallised from benzene–light petroleum (b. p. 60—80°) from which *2-ethoxy-6-methylpyridine 1-oxide* separated as plates, m. p. 102—103° (Found: C, 63·3; H, 7·3; N, 9·2. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2; N, 9·1%). Light absorption in ethanol: Maxima at 2610 A., $\varepsilon = 3600$, and 2990 A., $\varepsilon = 1500$. The *picrate* separated from ethanol as prisms, m. p. 88—89° (Found: N, 14·9. $C_{14}H_{14}O_9N_4$ requires N, 14·7%).

1-Hydroxy-2-keto-3-methyl-1 : 2-dihydropyridine.—A solution of 2-ethoxy-3-methylpyridine (9·5 g.) in glacial acetic acid (70 c.c.) was treated with hydrogen peroxide (100 vol.; 70 c.c.), and the solution maintained at 56° for 19 hours. The mixture was concentrated at 2 mm. (bath temperature below 30°) and the residue cooled to 0° and made alkaline with 3N-potassium hydroxide. The solution was then extracted with chloroform (6 × 35 c.c.), the extract dried (Na_2SO_4), and the solvent removed under reduced pressure. 2-Ethoxy-3-methylpyridine (0·9 g.) was removed by distillation. The residual viscous oil (2·26 g.) was dissolved in 3N-hydrochloric acid (25 c.c.), and the solution heated under reflux for 2 hours. The solution, which gave a deep cherry-red colour with aqueous ferric chloride, was evaporated under reduced pressure. The residue partly crystallised when kept. The mixture was triturated with ice-water and filtered. The crystalline solid (*A*), which gave a positive ferric chloride test, was collected and the filtrate made alkaline with sodium hydrogen carbonate and extracted with chloroform (3 × 40 c.c.). Acidification of the aqueous phase with hydrochloric acid, followed by extraction with chloroform (6 × 30 c.c.) and evaporation of the extract, yielded a solid which gave a positive ferric test. The solid was combined with solid (*A*) and sublimed at 80—85°/10^{-3} mm. The sublimate was crystallised from acetone to yield *1-hydroxy-2-keto-3-methyl-1 : 2-dihydropyridine* as needles, m. p. 138—139° (Found: C, 57·9; H, 5·6; N, 11·4; equiv., 130. $C_6H_7O_2N$ requires C, 57·6; H, 5·6; N, 11·2%; equiv., 125). The compound gave a copper salt, m. p. 276—278°, which separated from dioxan as needles.

1-Hydroxy-2-keto-4-methyl-1 : 2-dihydropyridine.—2-Ethoxy-4-methylpyridine 1-oxide (5·0 g.) was heated under reflux with hydrochloric acid (3N.; 100 c.c.) for 3 hours. The solution was evaporated under reduced pressure and the residue neutralised with sodium hydrogen carbonate solution. A slight excess of saturated copper acetate solution was added. The precipitated copper salt [2·0 g., m. p. 280° (decomp.)] was crystallised from dioxan from which it separated as prisms, m. p. 292° (decomp.). A solution of the copper salt (1·5 g.) in dioxan (100 c.c.) and water (100 c.c.) was treated with hydrogen sulphide. The mixture was evaporated to small bulk under reduced pressure and filtered (filter-aid). Evaporation of the filtrate to dryness gave a crystalline solid (0·7 g.) which, after crystallisation from acetone and sublimation at 100°/10^{-3} mm., gave *1-hydroxy-2-keto-4-methyl-1 : 2-dihydropyridine* (0·5 g.) as needles, m. p. 131—133° (Found: C, 57·7; H, 5·4; N, 10·8. $C_6H_7O_2N$ requires C, 57·6; H, 5·6; N, 11·2%).

Ethyl β-o-Nitrophenyl-α-methylacrylate.—A mixture of *o*-nitrobenzaldehyde (10·1 g.), propionic

anhydride (14 c.c.), and anhydrous sodium propionate (6·4 g.) was heated at 150° for 15 hours. The reaction mixture was poured into water, and the solid filtered off and extracted with dilute alkali. Acidification of the alkaline extract gave β-*o*-nitrophenyl-α-methylacrylic acid (9·4 g.) which separated from aqueous ethanol as needles, m. p. 194°. Edeleano (*Ber.*, 1887, **20**, 616) gives m. p. 208°, and Ranfaldi (*Rend. R. Accad. Scienze Fis. Mat. Napoli*, 1910, **3**, **16**, 226) gives m. p. 198° for this acid. A solution of the acid (4·2 g.) in dry ethanol (50 c.c.) containing dry hydrogen chloride (2·0 g.) was boiled under reflux for 2 hours. The mixture was evaporated under reduced pressure, the oil mixed with ice-water, and the mixture neutralised with concentrated sodium carbonate solution. The solid was collected, washed with water, and crystallised from aqueous ethanol, to give *ethyl β-o-nitrophenyl-α-methylacrylate* (4·5 g.) as prisms, m. p. 60° (Found: C, 61·7; H, 5·9; N, 5·6. $C_{13}H_{15}O_4N$ requires C, 61·3; H, 5·5; N, 6·0%).

1-*Hydroxy*-2-*keto*-3-*methyl*-1 : 2-*dihydroquinoline*.—Ethyl β-*o*-nitrophenyl-α-methylacrylate (4·3 g.) in ethanol (20 c.c.) was added to an aqueous ethanolic solution of ammonium sulphide prepared by saturating a mixture of ethanol (20 c.c.) and aqueous ammonia (*d*, 0·88; 5 c.c.) with hydrogen sulphide at 0°. The solution was heated in a closed vessel at 100° for 2 hours. The reaction mixture was evaporated to dryness under reduced pressure, and the solid extracted with warm 2N-sodium hydroxide solution. The combined extracts were acidified with dilute hydrochloric acid, and the yellow-brown solid (1·4 g.) extracted with cold 0·5N-sodium hydroxide. The insoluble residue, on treatment with water, gave 3-methylcarbostyril, m. p. 235° (1·1 g.); Ornstein (*Ber.*, 1907, **40**, 1095) gives m. p. 234—235°. Acidification of the alkaline extract with dilute hydrochloric acid gave a brown solid, m. p. 140—160° (200 mg.). The solid was twice sublimed at 140°/10^{-3} mm. to give 1-*hydroxy*-2-*keto*-3-*methyl*-1 : 2-*dihydroquinoline*, m. p. 182°, which separated from ethanol as prisms (Found: C, 68·4; H, 5·5; equiv., 180. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1%; equiv., 175). It gives a deep red colour in aqueous alcoholic ferric chloride.

2-*Ethoxy*-4-*methylquinoline* 1-*Oxide*.—A solution of 2-ethoxy-4-methylquinoline (3·3 g.; Knorr, *Annalen*, 1886, **236**, 102) in peracetic acid (80 c.c., prepared as described above) was maintained at 50° for 48 hours. The reaction mixture was evaporated (reduced pressure), the cold residue made alkaline with 3N-potassium hydroxide solution, and the mixture extracted with chloroform (6 × 35 c.c.). The dried (Na_2SO_4) extract was evaporated and the viscous oil dissolved in the minimum quantity of ethanol and treated with ethanolic picric acid. *2-Ethoxy-4-methylquinoline 1-oxide picrate* (2·1 g.) separated from ethanol as prismatic needles, m. p. 144—145° (Found: C, 50·0; H, 3·9; N, 12·9. $C_{18}H_{16}O_9N_4$ requires C, 50·0; H, 3·7; N, 13·0%). Decomposition of the picrate by the method of Burger (*J. Amer. Chem. Soc.*, 1945, **67**, 1615) gave 2-*ethoxy*-4-*methylquinoline* 1-*oxide* as slightly yellow plates, m. p. 61°, from acetone–light petroleum (b. p. 40—60°) (Found: N, 6·9. $C_{12}H_{15}O_2N$ requires N, 6·9%); yield, 550 mg.

1-*Hydroxy*-2-*keto*-4-*methyl*-1 : 2-*dihydroquinoline*.—A solution of 2-ethoxy-4-methylquinoline 1-oxide (260 mg.) in ethanol (5 c.c.) and hydrochloric acid (3N.; 6 c.c.) was heated under reflux for 2 hours. The mixture was evaporated to dryness. Sublimation of the residue at 120°/10^{-3} mm., followed by crystallisation from acetone, gave 1-*hydroxy*-2-*keto*-4-*methyl*-1 : 2-*dihydroquinoline* as needles, m. p. 225—227° (Found: C, 68·6; H, 5·1; N, 7·95; equiv., 167. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1; N, 8·0%; equiv., 175). A solution of the acid in ethanol gave a deep red colour with aqueous ferric chloride.

DL-*Alanine Hydroxamic Acid*.—A solution of hydroxylamine [from the hydrochloride (1·5 g.) and sodium (0·5 g.) in absolute methyl alcohol (50 c.c.)] was cooled to −10° and added slowly to a solution of DL-alanine methyl ester [from the hydrochloride (3·06 g.) and sodium (0·46 g.) in methyl alcohol (40 c.c.)] also at −10°. The mixture was kept at 0° overnight and concentrated to small bulk. The solid (1·4 g.) was collected and crystallised from aqueous ethanol, from which DL-*alanine hydroxamic acid* separated as small needles, m. p. 163—164° (Found: C, 34·7; H, 7·7; N, 27·2. $C_3H_8O_2N_2$ requires C, 34·6; H, 7·7; N, 26·9%). The acid gives a wine-red colour with aqueous ferric chloride, a property common to the hydroxamic acids described below.

By the same method, glycine hydroxamic acid was obtained as small prisms from aqueous methyl alcohol, m. p. 137° (decomp.) (Found: C, 27·1; H, 6·85. Calc. for $C_2H_6O_2N_2$: C, 26·7; H, 6·7%). Ley and Mannchen (*Ber.*, 1913, **46**, 754) give m. p. 107°, and Jones and Sneed (*J. Amer. Chem. Soc.*, 1917, **39**, 673) give m. p. 140° (decomp.).

DL-*Valine hydroxamic acid* separated from water as prisms, m. p. 180° (Found: C, 45·5; H, 9·3. $C_5H_{12}O_2N_2$ requires C, 45·5; H, 9·1%).

DL-iso*Leucine hydroxamic acid* formed very small needles, m. p. 171—172° (decomp.), from water (Found: C, 49·5; H, 9·3. $C_6H_{14}O_2N_2$ requires C, 49·3; H, 9·6%).

DL-*Phenylalanine hydroxamic acid* separated from water as very small plates, m. p. 180° (decomp.) (Found: C, 59·5; H, 6·4. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·7%).

p-*Aminobenzhydroxamic acid* separated as prismatic needles, m. p. 184—185° (decomp.), from methyl alcohol–ethyl acetate (Found: C, 55·6; H, 5·4; N, 18·7. $C_7H_8O_2N_2$ requires C, 55·3; H, 5·3; N, 18·4%).

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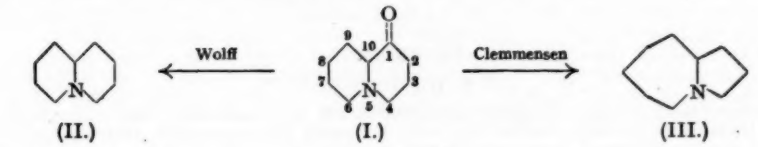
450. *The Clemmensen Reduction of Certain α-Amino-ketones and its Bearing on the Reduction of 1-Keto-octahydropyridocoline.*

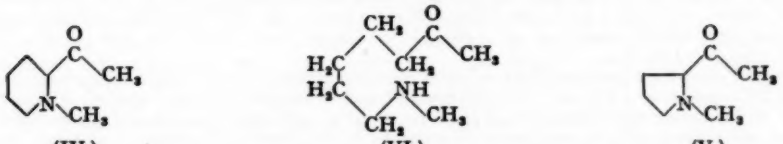
By G. R. Clemo, R. Raper, and H. J. Vipond.

Continuing our study of the anomalous Clemmensen reduction of 1-keto-octahydropyridocoline (I), we have prepared 2-acetyl-1-methylpiperidine and, from an examination of its reduction and that of 2-acetyl-1-methylpyrrolidine under similar conditions, offer an explanation of the peculiar rearrangement of (I).

In previous communications it was shown that whereas the Wolff reduction of 1-keto-octahydropyridocoline (I) yielded norlupinane (II) (*J.*, 1936, 1429), reduction by the Clemmensen method was anomalous, yielding an isomeric " base B " (*J.*, 1931, 437), and all substituted 1-keto-octahydropyridocolines so far studied have behaved similarly (*J.*, 1937, 1518; 1938, 1183, 1318). Prelog and Seiworth (*Ber.*, 1939, **72**, 1638) have since synthesised *bicyclo*[5 : 3 : 0]-1-azadecane (III) and shown it to be identical with " base B."



(II.) (I.) (III.)



(IV.) (VI.) (V.)

In order to study this peculiar rearrangement further it was decided to prepare the simpler but analogous ketone, 2-acetyl-1-methylpiperidine (IV), and examine its reduction by the Clemmensen and Wolff methods. Later 2-acetyl-1-methylpyrrolidine (V) was also examined.

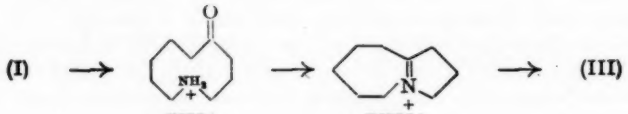
2-Acetylpyridine and its methosulphate could not be converted by fractional catalytic hydrogenation into the desired hexahydro-ketones, and (IV) was therefore prepared by complete hydrogenation of 2-acetylpyridine to 2-1′-hydroxyethylpiperidine, followed by *N*-methylation and oxidation with chromic acid, after the method of Hess and Corleis (*Ber.*, 1921, **54**, 3010). 2-Acetyl-1-methylpyrrolidine (V) has been prepared by a similar series of reactions. Hess, Merck, and Uibrig (*Ber.*, 1915, **48**, 1900) claimed to have obtained (V) by the action of formaldehyde on a hydrochloric acid solution of 2-1′-hydroxyethylpyrrolidine, but later stated that the base was more probably 5-methyl-3 : 4-trimethyleneoxazolidine. We have found that *N*-methylation of the above pyrrolidine alcohol by formaldehyde and formic acid proceeded normally to give *1-methyl-2-1′-hydroxyethylpyrrolidine*, chromic acid oxidation of which gave (V) identical with that described by H. King (*J.*, 1941, 337).

Wolff reduction of (IV) proceeded normally giving 1-methyl-2-ethylpiperidine. Clemmensen reduction, however, was anomalous, giving two products. One, a fully reduced secondary base, agreed in properties with the *N*-methylheptylamine described by von Braun (*Annalen*, 1911, **382**, 46) and its identity was confirmed by comparison of its derivatives with those of a synthetic specimen prepared from *methylheptylaniline*. 1 : 2-*Dimethylhexamethyleneimine* was also prepared, but no trace of it or of 1-methyl-2-ethylpiperidine could be isolated from the reduction mixture. The second product, a methyl ketone differing from the starting product, gave *N*-methylheptylamine on further reduction, and was shown by synthesis and comparison of derivatives to be *7-methylaminoheptan-2-one* (VI). This was readily prepared from the lactam of 5-methylaminohexoic acid and methylmagnesium iodide. Clemmensen reduction of (V) was also anomalous, yielding 1 : 2-dimethylpiperidine as sole product.

As Clemmensen reduction conditions had no effect on 1-methyl-2-1′-hydroxyethylpiperidine, (VI) is not produced by reduction to the alcohol followed by some type of " hydramine fission," but must be formed by preferential hydrogenolysis of the 1 : 2 N–C bond of (IV) (cf. the reduction of phenyl phenacyl sulphide, etc., von Braun and Weissbach *Ber.*, 1929, **62**, 2416). A normal Clemmensen reduction of the ε-amino-ketone (VI) then yields *N*-methylheptylamine. The anomalous Clemmensen reduction of (V) is also explained by a similar hydrogenolysis to

give 6-methylaminohexan-2-one, which, unlike (VI), spontaneously cyclises to 1 : 2-dimethyl-1 : 4 : 5 : 6-tetrahydropyridine (Lipp, *Ber.*, 1892, **25**, 2190; see also Adams and Mahan, *J. Amer. Chem. Soc.*, 1942, **64**, 2588). This in its turn is reduced to 1 : 2-dimethylpiperidine by tin and hydrochloric acid (Lipp, *loc. cit.*), and would thus be easily reduced under the more vigorous Clemmensen conditions.

The Clemmensen reduction of (I) is more closely related to that of (V) than to that of (IV). Preferential hydrogenolysis of the 10 : 5 C–N bond yields as intermediate the γ-amino-ketone (VII) which, as with other γ-amino-ketones (Craig, *J. Amer. Chem. Soc.*, 1933, **55**, 295), immediately cyclises giving, in this case in acid solution, the quaternary ion (VIII) which is readily reduced to (III).



(VII.) (VIII.)

Experimental.

(All m. p.s are uncorrected.)

2-1′-*Hydroxyethylpiperidine*.—Catalytic hydrogenation of 2-acetylpyridine (10 g.) in acetic acid (50 ml.), by Hess and Corleis's method (*loc. cit.*) but with platinic oxide (150 mg.) and hydrogen at 100 lb./sq. in. during 12 hours, gave the alcohol as a colourless oil (8·95 g.), b. p. 101—102°/23 mm. (Found : C, 65·0; H, 11·2. Calc. for $C_7H_{15}ON$: C, 65·1; H, 11·7%). The *picrate* crystallised from alcohol–ether in yellow cubes, m. p. 115—117° (Found : C, 43·7; H, 5·5. $C_7H_{15}ON,C_6H_3O_7N_3$ requires C, 43·4; H, 5·1%).

1-*Methyl*-2-1′-*hydroxyethylpiperidine*.—The following method is an improvement on that described by Hess and Corleis (*loc. cit.*). 2-1′-Hydroxyethylpiperidine (12·1 g.) was heated for 18 hours on the water-bath under reflux with formic acid (12·5 ml.; 90%) and aqueous formaldehyde (12·0 ml.; 40%). The residue, after evaporation, was made alkaline with 40% sodium hydroxide solution, extracted with chloroform, dried, and distilled, giving the tertiary amino-alcohol (10·94 g.), b. p. 80—89°/18 mm. (Found : C, 66·7; H, 12·1. Calc. for $C_8H_{17}ON$: C, 67·0; H, 12·0%). The *picrate* formed large lemon-yellow prisms, m. p. 91—92°, from ethyl acetate–light petroleum (Found : C, 44·4; H, 5·7. $C_8H_{17}ON,C_6H_3O_7N_3$ requires C, 45·1; H, 5·4%), and the *picrolonate* bright yellow prisms, m. p. 174—175° from alcohol (Found : C, 52·9; H, 6·4. $C_8H_{17}ON,C_{10}H_8O_5N_4$ requires C, 53·0; H, 6·2%).

2-*Acetyl*-1-*methylpiperidine*.—Oxidation of the above alcohol as described by Hess and Corleis (*loc. cit.*) gave (IV) (57%), b. p. 77—79°/14 mm. (Found : C, 68·1; H, 10·7; N, 10·1. Calc. for $C_8H_{15}ON$: C, 68·0; H, 10·7; N, 9·9%). The picrate had m. p. 121—123° and the *picrolonate* formed yellow glistening plates, m. p. 179—181°, from alcohol (Found : C, 53·5; H, 6·0. $C_{18}H_{23}O_6N_5$ requires C, 53·3; H, 5·7%).

Clemmensen Reduction of (IV).—(IV) (3·45 g.), amalgamated zinc (45 g.), and hydrochloric acid (75 ml.) were heated under reflux for 64 hours, the mixture was reduced to small volume, made alkaline, and distilled in steam. The initial steam-distillate (*A*) (30 ml.) contained a sparingly soluble basic oil, the later distillate (*B*) contained no oil but was strongly basic and gave a positive iodoform reaction. The dried ethereal extract of *A*, on distillation, gave *N*-methylheptylamine (0·52 g.), b. p. 166—168° (Found : C, 75·1; H, 15·3. Calc. for $C_8H_{19}N$: C, 74·4; H, 14·9%). The *picrolonate* formed pale yellow plates or prisms (from alcohol or water), m. p. 174° not depressed by an authentic specimen (Found : C, 54·8; H, 7·0. $C_8H_{19}N,C_{10}H_8O_5N_4$ requires C, 54·9; H, 6·9%). The picrate, obtained from ether, had m. p. 96—97° not depressed by an authentic specimen. Acidification and evaporation of *B* gave a hygroscopic hydrochloride from which a colourless basic oil (0·92 g.), b. p. 90—105°/20 mm. (bath temp.), was obtained by addition of alkali and distillation of the dried extract. This oil gave the reactions of a methyl ketone and was shown by comparison of derivatives to be 7-methylaminoheptan-2-one (VI). The *picrolonate* formed yellow prisms, m. p. 134—135°, from alcohol or water (Found : C, 53·3; H, 6·1. $C_8H_{17}ON,C_{10}H_8O_5N_4$ requires C, 53·0; H, 6·2%), and the *semicarbazone hydrochloride* very fine colourless prisms, m. p. 162—165°, from alcohol (Found : C, 45·7; H, 8·5. $C_9H_{20}ON_4,HCl$ requires C, 45·5; H, 8·9%).

Clemmensen Reduction of (VI).—(VI) (0·5 g.), amalgamated zinc (10 g.) and hydrochloric acid (25 ml.) were heated under reflux for 48 hours and the mixture was worked up as above, giving *N*-methylheptylamine (97 mg.) (picrolonate, m. p. 173°) and unreduced (VI) (236 mg.) (picrolonate, m. p. 134°).

Wolff Reduction of (IV).—(IV) (0·4 g.) and hydrazine hydrate (3 ml.) were heated under reflux for 18 hours, and the hydrazone was extracted with ether, dried, and heated in a sealed tube with sodium (0·5 g.) dissolved in alcohol (3 ml.) at 170—175° for 18 hours. The mixture was diluted with water, acidified, evaporated to small bulk, made alkaline with potassium carbonate, and extracted with ether. Addition of the dried ethereal solution to picric acid (0·65 g.) in ether gave 1-methyl-2-ethylpiperidine picrate (0·52 g.) which crystallised from water in needles, m. p. 173° (Found : C, 47·2; H, 5·7. Calc. for $C_8H_{17}N,C_6H_3O_7N_3$: C, 47·1; H, 5·6%).

N-*Methylheptylamine*.—Heptyl bromide (2·0 g.) and methylaniline (4·0 g.) were heated at 100° for 40 hours, the residue was made alkaline with excess of sodium hydroxide and extracted with ether, and the dried extract was distilled, giving *methylheptylaniline* (1·7 g.), b. p. 278—280°, as an almost colourless oil (Found : C, 81·5; H, 10·7. $C_{14}H_{23}N$ requires C, 81·9; H, 11·3%). The *picrate* formed

bright yellow prisms, m. p. 75°, from alcohol–water (Found: C, 55·7; H, 5·8. $C_{14}H_{23}N,C_6H_3O_7N_3$ requires C, 55·3; H, 6·0%). Sodium nitrite (0·37 g.) in water (1 ml.) was added during 20 minutes to a cooled solution of the above oil (0·6 g.) in hydrochloric acid (1·1 ml.) and water (1·1 ml.), giving the green nitroso-compound hydrochloride. This was separated after 1 hour and boiled under reflux, for 4 hours with 10% sodium hydroxide (20 ml.), the mixture distilled in steam, the distillate extracted with ether, and the dried extract distilled, to give *N*-methylheptylamine (0·13 g.), b. p. 75—85°/45—50 mm. (bath temp.). The picrate, m. p. 97°, as described by von Braun (*loc. cit.*), and the picrolonate, m. p. 174—175°, were identical with those described above.

7-*Methylaminoheptan*-2-*one* (VI).—The lactam of 5-methylaminohexoic acid (3·8 g.) in ether (30 ml.) was added to the Grignard reagent prepared from magnesium (0·8 g.) and methyl iodide (4·8 g.) in ether (40 ml.). After 3 hours the mixture was heated under reflux for ½ hour and kept overnight. Excess of 10% sulphuric acid was added to decompose the white complex, the aqueous layer separated made, alkaline, and extracted with ether, and the dried extract distilled and refractionated, to give the *ketone* (VI) (1·4 g.), b. p. 93—95°/16 mm. (Found: C, 67·1; H, 12·1. $C_8H_{17}ON$ requires C, 67·0; H, 12·0%). The picrolonate, m. p. 135°, and the semicarbazone hydrochloride, m. p. 163°, were identical with those described previously.

1 : 2-*Dimethylhexamethyleneimine*.—Lithium aluminium hydride (0·4 g.) in ether (20 ml.) was added to the lactam of 5-aminoheptoic acid (1·02 g.) in ether (30 ml.). After 3 days the complex was decomposed by 10% sulphuric acid, the aqueous layer was made alkaline and distilled in steam, and the distillate acidified with hydrochloric acid, evaporated to dryness, and recrystallised from acetone to give 2-methylhexamethyleneimine hydrochloride (0·53 g.), m. p. 156°, as colourless needles. The base from 0·5 g. of this hydrochloride was heated on the water-bath with formic acid (2 ml.) and aqueous formaldehyde (1·5 ml.; 40%) for 16 hours and worked up in the usual way, to give 1 : 2-dimethylhexamethyleneimine (210 mg.), b. p. 80—90°/50 mm. (bath temp.). The *picrate* formed light-yellow flat prisms, m. p. 233°, from alcohol (Found: C, 47·4; H, 6·0. $C_8H_{17}N,C_6H_3O_7N_3$ requires C, 47·2; H, 5·7%), and the *picrolonate* yellow needles, m. p. 162—164°, from alcohol (Found: C, 54·8; H, 6·7. $C_8H_{17}N,C_{10}H_8O_5N_4$ requires C, 55·2; H, 6·45%).

1-*Methyl*-2-1′-*hydroxyethylpyrrolidine*.—2-1′-Hydroxyethylpyrrolidine (1·8 g.), formic acid (4 ml.; 90%) and aqueous formaldehyde (4 ml.; 40%) were heated on the water-bath for 10 hours, hydrochloric acid (1·6 ml.) was added, the solution evaporated to dryness, made alkaline with 40% sodium hydroxide, and extracted with chloroform, and the extract dried and distilled, giving the tertiary *amino-alcohol* (1·6 g.), b. p. 70—72°/10 mm. (Found: C, 64·9; H, 11·2. $C_7H_{15}ON$ requires C, 65·1; H, 11·7%). The *picrate* formed bright yellow plates, m. p. 110—111°, from ethyl acetate or water (Found: C, 43·7; H, 5·2. $C_7H_{15}ON,C_6H_3O_7N_3$ requires C, 43·5; H, 5·0%).

2-*Acetyl*-1-*methylpyrrolidine* (V).—The above alcohol (0·6 g.) in acetic acid (18 ml.) was warmed to 70°, and chromic acid (0·9 g.) in water (0·9 ml.) and acetic acid (2·5 ml.) added dropwise during ½ hour. After a further 20 minutes at 80—90° hydrochloric acid (1·5 ml.) was added, the acetic acid removed, the residue made alkaline with potassium carbonate and extracted with ether, and the extract dried and distilled, giving the ketone (V) (170 mg.), b. p. 50—55°/9 mm. (bath temp.), as a colourless unstable oil. The picrate formed yellow plates on precipitation from ether but recrystallised from water in yellow prisms, m. p. 117—118° (Found: C, 43·5; H, 4·3. Calc. for $C_7H_{13}ON,C_6H_3O_7N_3$: C, 43·8; H, 4·5%).

Clemmensen Reduction of (V).—(V) (90 mg.), amalgamated zinc (2 g.), and hydrochloric acid (4 ml.) were boiled under reflux for 40 hours, the mixture was made alkaline with 10% sodium hydroxide solution and steam-distilled into dilute hydrochloric acid which was subsequently evaporated to dryness, made alkaline, and extracted with ether. The dried extract was added to picric acid (180 mg.) in ether, giving 1 : 2-dimethylpiperidine picrate (85 mg.), m. p. 240° after recrystallisation from water, not depressed by an authentic specimen (Found: C, 45·6; H, 5·2. Calc. for $C_7H_{15}N,C_6H_3O_7N_3$: C, 45·5; H, 5·3%).

One of us (H. J. V.) wishes to thank the Department of Scientific and Industrial Research for a maintenance allowance.

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[*Received, April 8th*, 1949.]

NOTE.

The Production of Amidines from Cyanides and Ammonium Salts. By J. CYMERMAN, J. W. MINNIS, P. OXLEY, and W. F. SHORT.

IN order to ascertain whether salts other than sulphonates (*J.*, 1946, 147) and thiocyanates (*J.*, 1947, 390) can be used in the preparation of amidines, we have heated a variety of ammonium salts with two reactive cyanides, and have also investigated the stability of a number of salts of *p*-methylsulphonylbenzamidine. No amidine could be isolated when *p*-sulphonamidophenyl cyanide was heated at various temperatures within the range 200—250° with ammonium chloride, sulphate, phenoxide, picrate, sulphamate, selenate, or diammonium hydrogen phosphate. A vigorous reaction occurred at 235° with ammonium hydrogen selenate and most of the cyanide was hydrolysed to a mixture of *p*-sulphonamidobenzamide and *p*-sulphonamidobenzoic acid. The sensitive Fuller reaction (*Nature*, 1944, **154**, 773; *Biochem. J.*, 1945, **39**, 99) was used to detect the formation of amidine when *p*-methylsulphonylphenyl cyanide was heated for 6½ hours with various ammonium salts (3 mols.) at a series of temperatures ranging from 100° to 245°. Completely negative results were obtained with ammonium bromide, hydrogen sulphate, laurate, trichloroacetate, and diammonium hydrogen phosphate, but a positive Fuller reaction

was obtained after heating the cyanide at 170° with ammonium nitrate for 6 hours. After 6½ hours at 130° ammonium formate gave a 25% yield of *N*-formyl-*p*-methylsulphonylbenzamidine, isolated as *picrate*. *p*-Methylsulphonylbenzamidine was obtained by heating the corresponding cyanide with ammonium acetate or fluoride, variations in the reaction temperature having a marked effect on the yield of amidine (see below). *p*-Chlorobenzamidine was obtained in 61% yield by passing ammonia into a mixture of *p*-chlorophenyl cyanide, ammonium benzenesulphonate, and ammonium acetate at 130° (compare Part VIII; *J.*, 1948, 303).

N-*Formyl*-p-*methylsulphonylbenzamidine*.—A mixture of *p*-methylsulphonylphenyl cyanide (1·8 g.) and ammonium formate (1·9 g.; 3 mols.) was stirred and heated at 131° until the intensity of the colour reaction with Fuller's reagent reached a maximum (6½ hours). The homogeneous melt was cooled, diluted with ice-water (20 c.c.), and stirred with 10N-sodium hydroxide (15 c.c.) at 0°. The solid was collected, and its aqueous suspension made acid to Congo-red with hydrochloric acid. *p*-Methylsulphonylphenyl cyanide (1·1 g.), m. p. and mixed m. p. 142°, was recovered, and addition of alcoholic picric acid to the filtrate afforded N-*formyl*-p-*methylsulphonylbenzamidinium picrate*, m. p. 285° (Found: N, 15·65. $C_{15}H_{13}O_{10}N_5S$ requires N, 15·4%); yield, 0·9 g., 25%.

p-*Methylsulphonylbenzamidine*.—(1) *p*-Methylsulphonylphenyl cyanide (1·81 g.) and ammonium fluoride (1·11 g.; 3 mols.) were heated at various temperatures for 6½ hours and the amidine, separated from the unchanged cyanide by extracting with dilute acid, was isolated as picrate, m. p. and mixed m. p. 263°. The effect of temperature on the yield of amidine was as follows:

Temp.	131°	153°	186°	220°
Recovered cyanide, %	100	77	72	66
Amidinium picrate, %	0	19	26	19

(2) *p*-Methylsulphonylphenyl cyanide (1·81 g.) and ammonium acetate (2·31 g.; 3 mols.), similarly heated for 6½ hours, both (*a*) alone and (*b*) in presence of acetamide (1·77 g.; 3 mols.), gave the following yields of amidine:

Temp.	131°	153°	186°
Recovered cyanide, %	(*a*) 77; (*b*) 66	(*a*) 77; (*b*) 66	(*a*) 88; (*b*) 83
Amidinium picrate, %	(*a*) 13; (*b*) 20	(*a*) 7; (*b*) 16*	(*a*) —; (*b*) 7

* After 3 hours at 153° the yield was 8%.

p-*Methylsulphonylbenzamidinium Salts*.—*Fluoride*. This *salt* was obtained by neutralising an aqueous suspension of the amidine to brilliant-yellow with hydrofluoric acid and adding acetone to precipitate the hydrated salt, m. p. 188—189° (Found, in a sample dried at 100°: N, 12·65. $C_9H_{11}O_2N_2FS$ requires N, 12·8%). When the fluoride was heated for 10 minutes at 190—195° ammonia was evolved, and 16% of the amidine was recovered as picrate, m. p. and mixed m. p. 263°. After 30 minutes' heating at 200—205°, 5% of the amidine was recovered.

Acetate. Prepared from its constituents and crystallised from boiling water, this *salt* had m. p. 232—233° (Found: N, 11·0. $C_{10}H_{14}O_4N_2S$ requires N, 10·9%).

Benzoate. Prepared from its constituents in aqueous alcohol and crystallised from water, the *benzoate* had m. p. 232—233° (decomp.) (Found: N, 8·8. $C_{15}H_{16}O_4N_2S$ requires N, 8·75%). After 10 minutes' heating at 236—238°, 2% of the amidine was recovered, the rest being decomposed to *p*-methylsulphonylphenyl cyanide, m. p. and mixed m. p. 141—142°.

Trichloroacetate. This *salt* separated from water in crystals, m. p. 178—179° (Found: N, 7·9. $C_{10}H_{11}O_4N_2Cl_3S$ requires N, 7·75%); it was completely decomposed when heated at 186° for 10 minutes, and the recovered cyanide had m. p. 141—142°.

The *sulphate*, prepared similarly, had m. p. 264—266° (Found: N, 11·3. $C_{16}H_{22}O_8N_4S_3$ requires N, 11·3%).

p-*Chlorobenzamidine*.—*p*-Chlorophenyl cyanide (2·8 g.), ammonium acetate (4·6 g.), and ammonium benzenesulphonate (3·5 g.) were heated at 131° for 6½ hours, ammonia being passed into the molten mixture. The product afforded unchanged *p*-chlorophenyl cyanide (0·5 g.), m. p. 95°, and *p*-chlorobenzamidinium picrate, m. p. 256° (decomp.), in 61% yield (4·75 g.). The picrate is described in Part II (*J.*, 1947, 766), and the corresponding chloride has been prepared by Ekeley, Tieszen, and Ronzio (*J. Amer. Chem. Soc.*, 1935, **57**, 381).—RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO., LTD., NOTTINGHAM. [*Received, May 27th*, 1948.]

PRESIDENTIAL ADDRESS.

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Concerning Amino-acids, Peptides, and Purines.

By SIR IAN HEILBRON, D.S.O., LL.D., F.R.S.

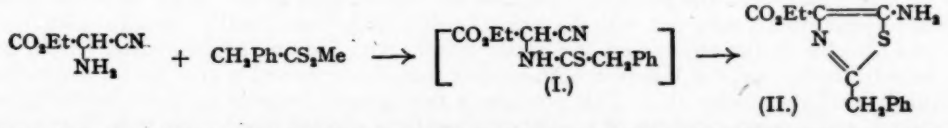
INTRODUCTION.

DURING an attack, with Dr. A. H. Cook and younger colleagues, upon the difficult problem of investigating possible routes for the synthesis of penicillin or biologically active analogues of it, a new reaction of α-amino-nitriles was discovered which provided an easy route to many hitherto inaccessible thiazole derivatives. At the same time some quite unexpected aspects of the chemistry of these compounds was revealed. Although the thiazole ring exhibits aromatic character, we have found in fact that suitably substituted thiazoles undergo a series of remarkable transformations, with the formation of further heterocyclic systems, hitherto accessible only with difficulty, whilst again other members undergo ready ring-fission leading to α-amino-acids or near derivatives thereof. This versatility has been turned to advantage in developing during the past three years new and general synthetic routes to amino-acids, peptides, and purines, the outstanding merit of which is that almost every step may be conducted at room temperature. The purpose of this Address then is to survey some of these new and flexible methods and to draw attention to the unity behind many diverse naturally occurring nitrogenous compounds, which has hitherto mostly escaped notice.

At the outset I would like to emphasize that the work I am about to describe is a team effort in which Dr. Cook has been responsible for the detailed development of the researches as a whole. I would like also to mention the name of Dr. A. L. Levy who has been concerned with the project since its initiation and has largely contributed to the work on peptides, and also that of Dr. J. D. Downer for his work in connection with the development of the purine syntheses. Finally I gratefully record the loyal co-operation of many others including Drs. J. D. Billimoria, C. W. Capp, J. R. Catch, R. Chatterjee, G. Harris, S. F. Macdonald, A. P. Mahadevan, G. Shaw, E. S. Stern and, among more recent collaborators, Messrs. A. C. Davis, G. D. Hunter, J. R. A. Pollock, E. Smith, and G. H. Thomas.

SOME 5-AMINOTHIAZOLES AND THEIR REACTIONS.

The origin of the researches under discussion was the observation that, when ethyl amino cyanoacetate was stood with methyl phenyldithioacetate, methanethiol was evolved. In place, however, of the expected thioamide (I), a basic product was obtained, in excellent yield,



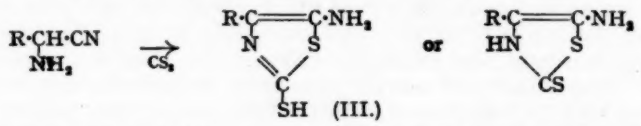
which proved to be ethyl 5-amino-2-benzylthiazole-4-carboxylate (II) (Bentley, Catch, Cook, Heilbron, and Shaw, CPS 267). This has now been found to be representative of a general reaction between α-amino-nitriles and dithio-acids or their esters (Studies in the Azole Series, Part I, Cook, Heilbron, and Levy, *J.*, 1947, 1594; Part XVII, Cook, Heilbron, and Smith, *J.*, this vol. p. 1440). Thioamides are undoubtedly intermediates in this synthesis and have been isolated in certain cases.

Whilst 2-aminothiazoles are among the best known of all thiazole compounds, 5-aminothiazoles have hitherto been almost unknown. It is only recently that Jensen and Hansen (*Dansk Tidskr. Farm.*, 1943, **17**, 189) and Ganapathi and Venkataraman (*Proc. Indian Acad. Sci.*, 1945, **22**, A, 343), stimulated by the valuable properties of sulphathiazole, a 2-aminothiazole derivative, prepared comparable 5-aminothiazole compounds by using orthodox reactions such as the Curtius degradation of ethyl thiazole-5-carboxylates; however, these reactions were found to be not generally applicable and the starting materials were often difficultly accessible. The only other previously known 5-aminothiazoles were " chrysean " and its derivatives. " Chrysean " was first obtained in 1874 by Wallach as a product of the interaction of hydrogen sulphide and aqueous sodium cyanide (Beilstein's " Handbuch," Vol. **27**, 334; Arnold and Scaife, *J.*, 1944,

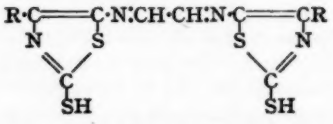
103), its formulation as 5-amino-2-thiocarbamylthiazole having only now received confirmation from the work of Erlenmeyer, Mengisen, and Prijs (*Helv. Chim. Acta*, 1947, **30**, 1865).

The 5-aminothiazoles are essentially aromatic in character, resembling the deactivated *o*- and *p*-nitroanilines. Thus they can be diazotised, acylated, condensed with aldehydes or ketones to give Schiff's bases, etc. Like the nitroanilines they lose the amino-group as ammonia by hydrolysis. This grouping exerts an activating influence on thiazoles containing an unsubstituted 4-position, where coupling with diazonium salts is readily effected.

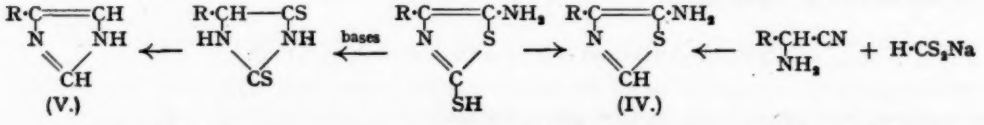
More arresting than the compounds so far described are the related compounds obtained by the use of carbon disulphide as a thioacylating agent in place of a dithio-acid or -ester. Interaction with α-amino-nitriles occurs at room temperature to afford the highly crystalline 5-amino-2-mercaptothiazoles (III) (Part II, Cook, Heilbron, and Levy, *J.*, 1947, 1598; Part X, Cook,



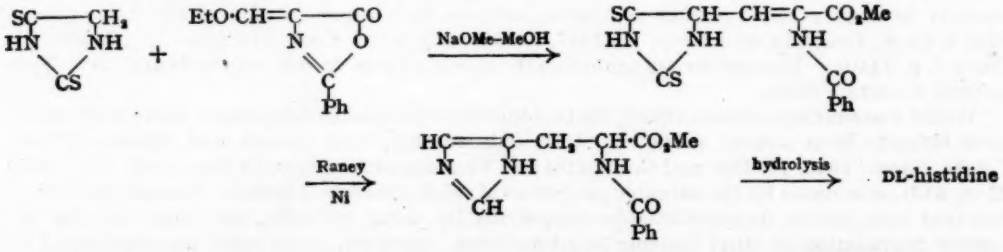
Heilbron, and Stern, *J.*, 1948, 2031). In many ways these bases afford functional derivatives which call for no particular mention, while in other ways their behaviour differs from that which might be expected. For instance, they condense with aldehydes and ketones with remarkable ease to give the highly crystalline Schiff's bases. Noteworthy is the reaction with glyoxal whereby deep red bis-compounds are obtained :



the appearance of which offers a valuable diagnostic test for 5-aminothiazoles. The most interesting reaction of the 5-amino-2-mercaptothiazoles is that which occurs when these compounds are allowed to react with aqueous alkalis or organic bases : molecular rearrangement ensues with formation of the isomeric 2 : 4-dithiohydantoins. The dithiohydantoins are strongly

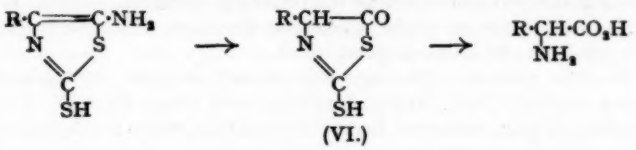


acidic substances from which the sulphur atoms can be readily removed with Raney nickel. It may be noted that when the precursor thiazoles are treated with Raney nickel only the extra-nuclear sulphur atom is removed, with the formation of 5-aminothiazoles (IV) identical with those obtained directly by the interaction of α-amino-nitriles with sodium dithioformate. With the rearranged dithiohydantoins, however, both sulphur atoms are removed to give the corresponding 5(4)-substituted glyoxalines (V). This provides a new general route to such monosubstituted glyoxalines, and a novel synthesis of DL-histidine has been effected along these lines (Davis and Levy, *J.*, in the press) :



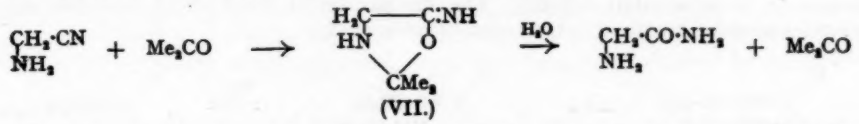
I revert now to the chemical transformation of the 5-amino-2-mercaptothiazoles : they are readily broken down by dilute mineral acids to give the corresponding α-amino-acids in good yield. This is frequently an improvement when preparing amino-acids by the Strecker route as the highly crystalline thiazoles can usually be isolated more conveniently and in better yield

than the free amino-nitriles (see, for example, Catch, Cook, Graham, and Heilbron, *J.*, 1947, 1609). The fact that α-amino-amides are not isolated from this hydrolysis suggests that the



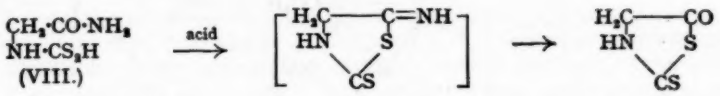
(VI.)

initial reaction is removal of the 5-amino-group to give a thiazolone (VI) which then loses carbon disulphide. Indeed the parent member of this aminothiazole series is converted into 2-mercaptothiazole (VI; R = H) with remarkable ease. The last compound, itself an isomeride of rhodanine, is the first representative of a new class of heterocyclic substances, and is more conveniently prepared by a series of novel reactions which were discovered accidentally during a study of the liberation of aminoacetonitrile from its sulphate (Part III, Cook, Heilbron, and Levy, *J.*, 1948, 201). It was found that suspending the sulphate in acetone and treating the suspension with sodium ethoxide, followed by carbon disulphide, unexpectedly gave a salt of the dithiocarbamic acid from aminoacetamide (VIII), which on acidification gave 2-mercaptothiazolone. It subsequently transpired that the mechanism of these surprising reactions involved condensation of the aminonitrile with the solvent, acetone, to give in quantitative yield a crystalline solid, probably 5-imino-2 : 2-dimethyloxazolidine (VII), which was readily split, again quantitatively, by cold water to aminoacetamide and acetone :



(VII.)

These reactions have since been found to be general with respect to both the amino-nitrile and the ketone components. Finally dithiocarbamates from α-amino-amides generally have been found to afford thiazolones on acidification, *e.g.*,

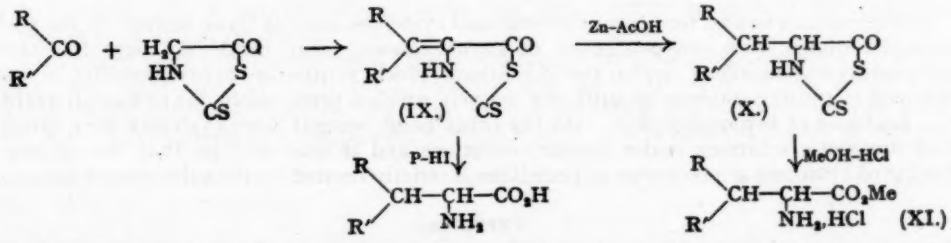


(VIII.)

AMINO-ACIDS.

A number of features of the parent thiazolone just described have been turned to advantage in devising new syntheses of α-amino-acids and their near derivatives.

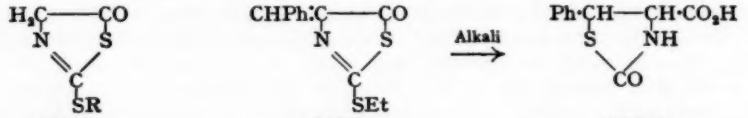
Like rhodanine, hydantoin, and 2-substituted oxazolones, 2-mercaptothiazolone exhibits a reactive methylene group which may be condensed with a wide variety of aldehydes and ketones. Though these condensations may in many instances be carried out in hot acid media, it is a special feature of the thiazolones that such condensations are very easily effected in presence of inorganic or organic weak bases, the alkylidene or arylidene products (IX) being obtained in excellent yield substantially at room temperature (Billimoria and Cook, Part XIX, in the press) :



The double bond in these compounds can be reduced by means of zinc and acid, thereby giving substituted derivatives (X) of the parent compound. Although the whole range of thiazolones has not yet been fully studied, enough has been established to show that their ring stability is generally similar to that of the unsubstituted thiazolone. For example, they are converted by

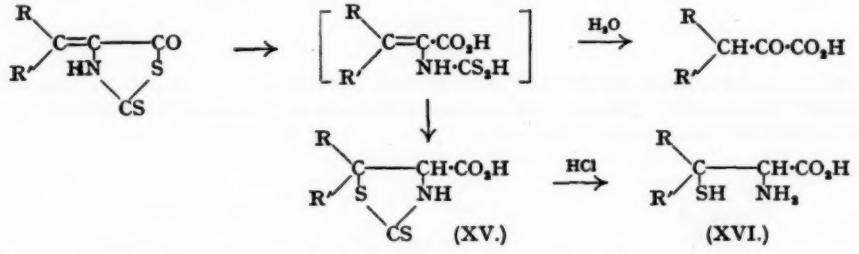
means of methanolic hydrogen chloride into α-amino-acid ester hydrochlorides (XI). Moreover, the unsaturated thiazolone derivatives may be reduced and the ring opened in a single stage. Thus with phosphorus and hydrogen iodide as the reducing agent the formation of α-amino-acids is readily achieved. In this manner β-phenylalanine, tyrosine, valine, leucine, norleucine, and other amino-acids have been obtained in good yield.

In addition to the free mercaptothiazolones a variety of 2-alkylthiothiazolone derivatives (XII) had earlier been studied (Cook, Harris, Heilbron, and Shaw, Part IV, *J.*, 1948, 1056) with generally similar results. It had, moreover, been observed that, when 2-ethylthio-4-benzylidene-5-



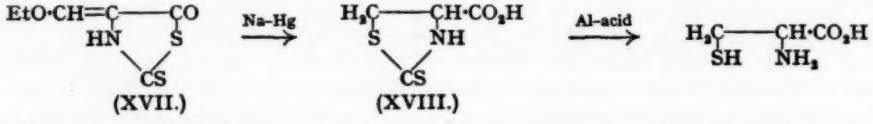
(XII.) (XIII.) (XIV.)

thiazolone (XIII) was treated with aqueous ethanolic alkali, 5-phenyl-2-thiazolidone-4-carboxylic acid (XIV) was obtained. On acid hydrolysis the latter product afforded β-phenylcysteine (Cook, Harris, and Heilbron, Part V, *J.*, 1948, 1060), and a precisely similar series of reactions was used to provide ββ-dimethylcysteine or penicillamine (Catch, Cook, Harris, and Heilbron, CPS 678). It has recently been observed that 2-mercapto-4-alkylidene- or -4-arylidene-thiazolones similarly rearrange in presence of sodium hydroxide, sodium alkoxides, or primary or secondary amines, giving respectively 5-substituted 2-thiothiazolidone-4-carboxylic acids (XV), esters, or *N*-substituted or unsubstituted amides. The mechanism of their origin was indicated by the formation in aqueous media of substituted pyruvic acids :



(XV.) (XVI.)

When the thiothiazolidones were heated with hydrochloric acid they were converted into substituted cysteines (XVI), many of which have so been synthesised. Cysteine itself was obtained by a modified procedure whereby 2-mercaptothiazolone was condensed with ethyl orthoformate to give an ethoxymethylene derivative (XVII), which was reduced and rearranged to the desired thiothiazolidone (XVIII) by sodium amalgam (Chatterjee, Cook, Heilbron, and Levy, Part VII, *J.*, 1948, 1337).



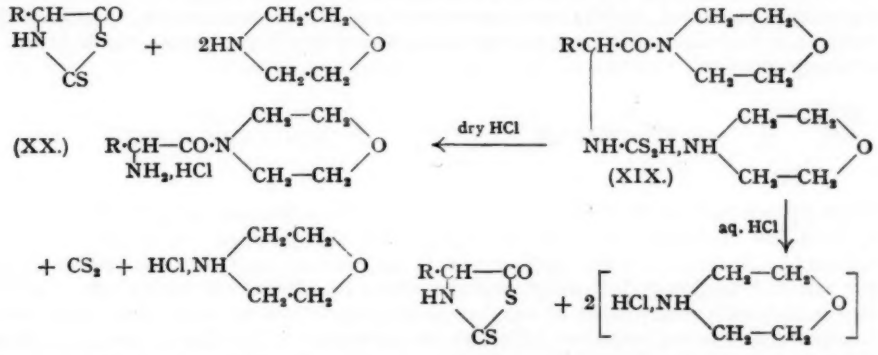
(XVII.) (XVIII.)

It is interesting to find that certain substituted cysteines, such as those derived by the above-mentioned routes from *cyclo*pentanone or *cyclo*hexanone, when condensed with 2-benzyl-4-ethoxymethyleneoxazolone under the conditions which synthesise benzylpenicillin in small yield, lead to the development of antibiotic activity which is presumably due to a small quantity of an analogue of benzylpenicillin. On the other hand, several β-arylcysteines have failed to afford antibiotic solutions under similar conditions and it may well be that the efficacy of substituted cysteines as precursors of penicillins is strictly limited by the substituents present.

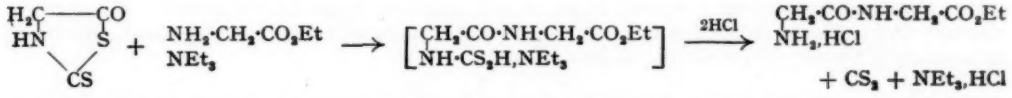
Peptides.

Whereas the reactions just outlined had their origin in the reactive methylene group of 2-mercapto-5-thiazolone or its near derivatives, those now to be reviewed depend more immediately on cleavage of the heterocyclic ring in these compounds. The earlier section of this work has been carried out entirely by Dr. A. L. Levy.

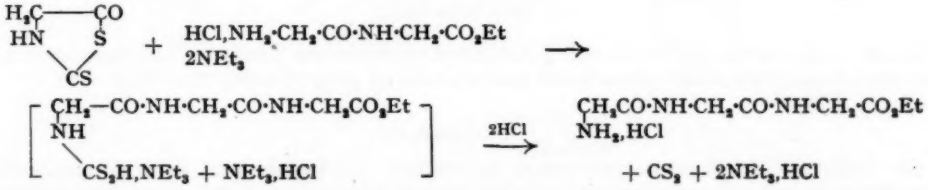
2-Mercapto-5-thiazolones are formally dithio-analogues of the carboxy-anhydrides of α-amino-acids, which have excited interest in many laboratories in recent years because of their ability to give rise to polypeptides. Such carboxy-anhydrides are mostly unstable and hardly permit of their ring-fission in a controlled manner except under acid conditions. By contrast the 2-mercaptothiazolones, while more stable, are still readily attacked by primary or secondary bases to give dithiocarbamate salts derived from the corresponding amide (*e.g.*, XIX) :



Whereas in presence of aqueous acids these revert to the original thiazolones, under anhydrous conditions carbon disulphide is liberated and the corresponding amides (XX) are obtained. By use of α-amino-esters this behaviour has, with modifications, been developed into a new method for the controlled synthesis of polypeptides. This may best be illustrated by reference to an example.

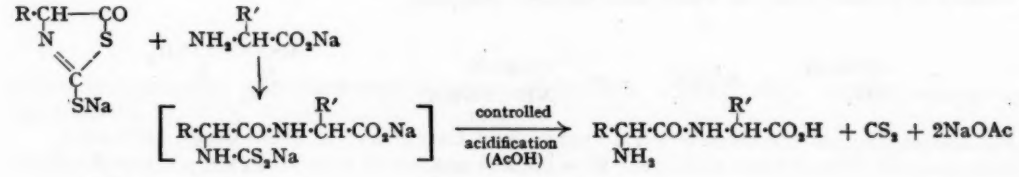


Treatment of 2-mercaptothiazolone with one equivalent each of glycine ethyl ester and triethylamine in ethanol causes rapid ring fission. Acidification of the solution with ethanolic hydrogen chloride without isolation of the intermediate dithiocarbamate salt leads to the separation of the hydrochloride of glycylglycine ethyl ester. This product is then used directly in presence of an additional molar quantity of triethylamine, liberating the dipeptide free base *in situ*, to attach another glycyl unit.



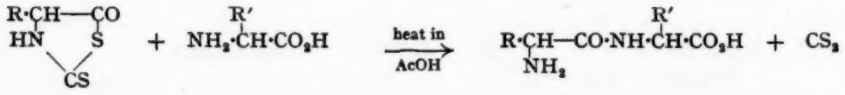
By further repetition of the operation the tetra- and penta-peptide esters have been prepared in crystalline form and in good yield.

With use of 2-mercaptothiazolone on the one hand, the method is applicable on the other to amino-esters generally, in both their racemic and their optically active forms. With 4-substituted 2-mercaptothiazolones the yields have so far been less satisfactory because acidification of the intermediate dithiocarbamate salt tends, even in non-aqueous media, to regenerate



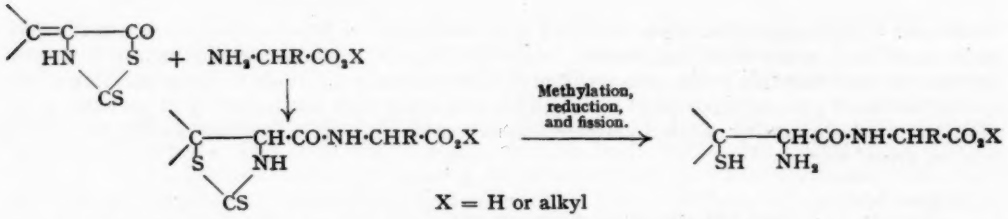
the original thiazolone. Incidentally, amino-acid and peptide ester hydrochlorides are very suitable for analysis by partition chromatography on paper, the above glycylpeptides, for example, forming a well-spaced series with butanol–acetic acid as the mobile phase, whereas under the same conditions the free peptides are closely crowded together.

The reaction of thiazolones with α-amino-acids in alkaline solution can conveniently be followed by measuring the marked decrease in pH which accompanies ring-fission. When acidification is then effected under carefully controlled conditions (*e.g.*, acetic acid at 70°) the desired peptide is produced, mixed invariably with its component amino-acids. Cation exchange resins have been found suitable for the separation of such mixtures, and for the isolation of the crystalline peptide.



A simpler procedure involves heating a thiazolone with an α-amino-acid in glacial acetic acid or water for a few moments; the peptide is produced, though again contaminated with some free amino-acid. Unlike the ester method, this is least satisfactory with the parent thiazolone (R = H), some of the lower polyglycyl peptides being simultaneously produced. Once again paper chromatography has proved of very great assistance in these studies for demonstrating the presence of the expected peptides. Though the tendency of the dithiocarbamic derivatives of peptides to lose the terminal amino-acid unit as a thiazolone may limit the synthetic usefulness of the series of reactions, it may in complementary fashion provide a simple means of recognising those terminal units in preformed peptides; this possibility is at present under investigation.

It will be recalled that 2-mercapto-4-alkylidene- or 2-mercapto-4-arylidene-thiazolones undergo rearrangement in presence of bases to give derivatives of 2-mercaptothiazolidone-4-carboxylic acids from which a variety of α-amino-β-mercapto-acids was prepared. This general reaction now appears to be of still more useful flexibility in that the rearrangement is brought about simply by salts or esters of α-amino-acids.

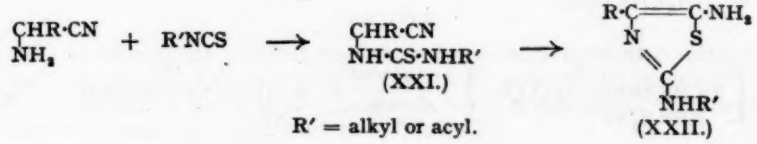


X = H or alkyl

In this way peptides derived from substituted cysteines are obtained, and their interest as precursors of penicillins and glutathione analogues is at present being examined.

Purines.

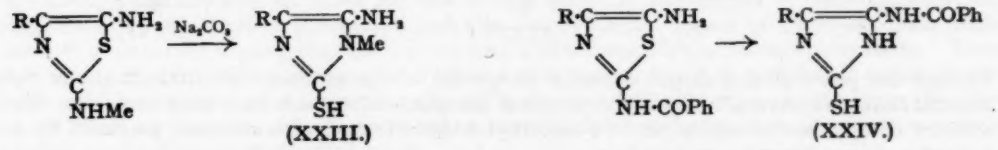
The facility with which derivatives of glyoxalines can be obtained from α-amino-nitriles suggested that such glyoxalines might form the means of preparing purines in variety by closing the six-membered ring on to the 4 : 5-positions of the glyoxaline system. A few syntheses of this general kind are known (literature : Sarasin and Wegmann, *Helv. Chim. Acta*, 1924, **7**, 713; Montequi, *Anal. Soc. Fís. Quím.*, 1927, **25**, 182; Mitter and Chatterjee, *J. Ind. Chem. Soc.*, 1934, II, 867; Allsebrook, Gulland and Story, *J.*, 1942, 232; Mann and Porter, *J.*, 1945, 751; Baxter and Spring, *ibid.*, p. 232), but difficultly accessible intermediates were used. The work now to be reviewed has entirely overcome such disadvantages and provides a route for the synthesis of a great variety of purines, many of which were hitherto unknown.



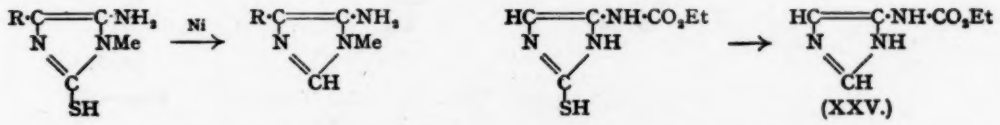
R′ = alkyl or acyl.

As a link between the 5-aminothiazoles of the earlier work and the desired 5-aminoglyoxalines, the action of *iso*thiocyanates on α-amino-nitriles has been studied. In all the cases examined (R = H, Me, Ph, CO_2Et, or $CO{\cdot}NH_2$; R′ = Me, Ph, COPh, or CO_2Et) the ultimate product is a substituted 2 : 5-diaminothiazole (XXII); the acyclic thioureas (XXI) are intermediates and have been isolated in certain instances. This new series of 5-aminothiazoles is in many respects similar to that already discussed.

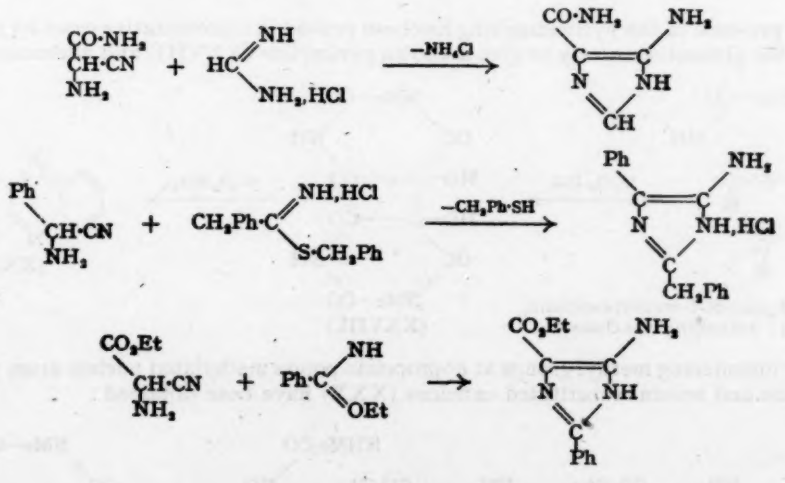
When warmed with aqueous sodium carbonate, these 5-aminothiazoles undergo molecular rearrangement to give 5-amino-2-mercaptoglyoxalines, the R′ grouping being finally located at position 1 or 5 according to whether it is a hydrocarbon residue (XXIII) or an acyl group (XXIV), respectively. 1-Acyliminazoles may be first formed in the latter case, and in view of the known



lability of such compounds it is probable that the acyl group then migrates to the more basic centre. Both types of rearrangement product are readily desulphurised by Raney nickel, and where R = H and R′ = CO_2Et (XXII) the nature of the rearrangement was confirmed by the emergence of the known 5-carbethoxyaminoglyoxaline (XXV) (Cook, Downer, and Heilbron, Parts VI and IX, *J.*, 1948, 1262, 2028; Capp, Cook, Downer, and Heilbron, Part VIII, *J.*, 1948, 1340; Cook, Heilbron, and Smith, Part XVII, p. 1440).



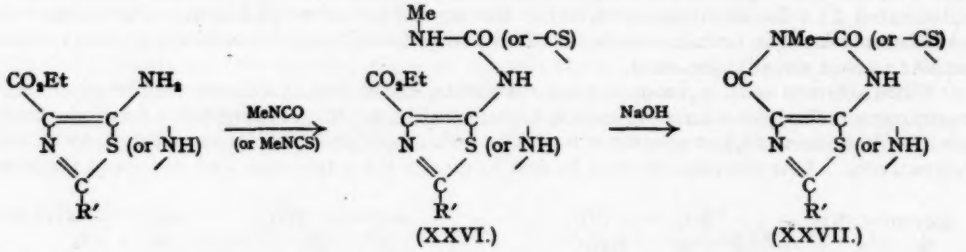
Still other and more direct syntheses of 5-aminoglyoxalines, which do not involve the intermediate formation of thiazoles, have been devised by condensing α-amino-nitriles with imino esters, thioimino-esters, or amidines. The following examples are representative of the compounds thus prepared (Cook, Davis, Heilbron, and Thomas, Part XIV, this vol., p. 1071) :



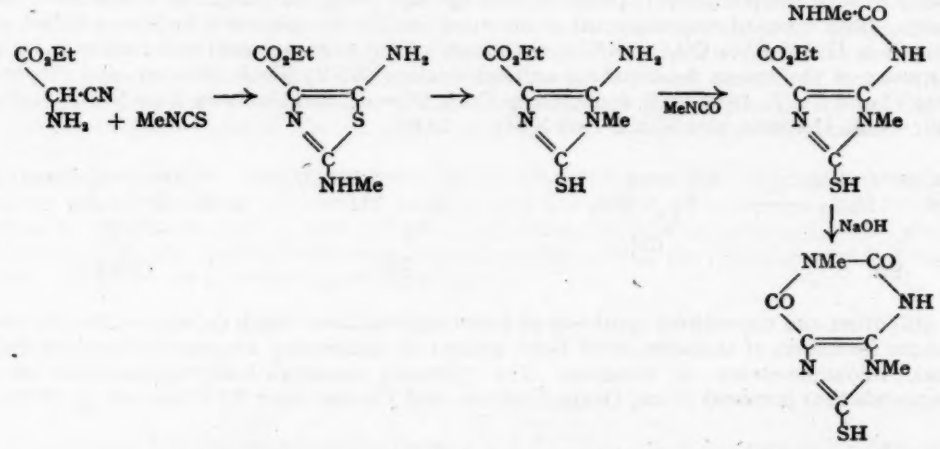
Like the thiazoles described earlier these glyoxalines reacted with *iso*thiocyanates or *iso*cyanates.

Somewhat surprisingly it was found that when ethyl 5-ureido-or 5-thioureidoazole-4-carboxylates (*i.e.*, glyoxalines or thiazoles) (XXVI) were allowed to stand in cold dilute aqueous

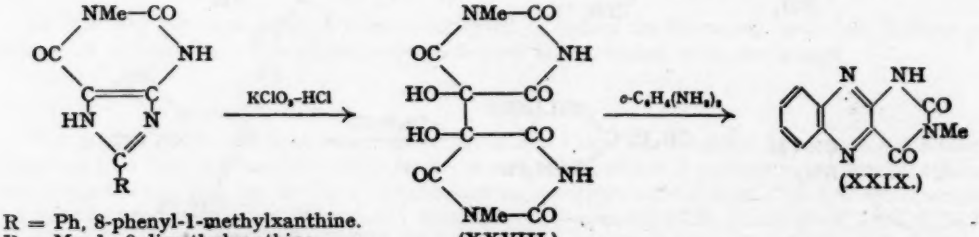
sodium hydroxide the elements of ethanol were eliminated, with simultaneous cyclisation to the corresponding purines or thiazolopyrimidines (XXVII), *e.g.*,



Though the physical and simple chemical properties of the products left little doubt of their bicyclic character, several independent proofs of the course of reaction have been revealed. Thus a direct comparison of authentic 1 : 9-dimethyl-8-thiouric acid with material prepared by the following stages shows their identity :



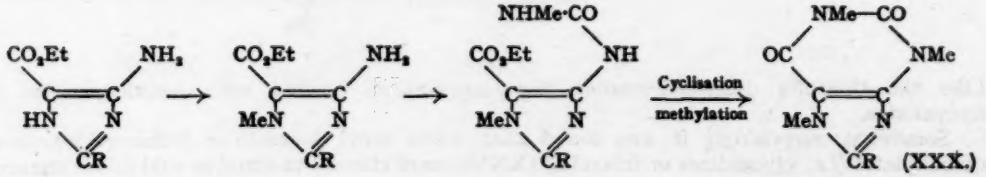
Again the presence of the pyrimidine ring has been proved in representative cases by oxidatively removing the glyoxaline moiety to give a known pyrimidine (XXVIII) and alloxazine (XXIX).



R = Ph, 8-phenyl-1-methylxanthine.
R = Me, 1 : 8-dimethylxanthine.

(XXVIII.)

Finally by introducing methyl groups at appropriate points methylated purines arise, and in this way caffeine and several substituted caffeines (XXX) have been obtained :



(Cook, Davis, Downer, Heilbron, Macdonald, Mahadevan, and Thomas, Parts XII—XIV, this vol., pp. 1064—1074).

Recent developments in another field have lent an added significance to this work. 5-Amino-4-carbamylglyoxaline mentioned above appears to be an intermediate in the bacterial synthesis of purines and accumulates in cultures of *E. coli* undergoing sulphonamide bacteriostasis (Shrive, Ackermann, Gordon, Getzendaner, and Eakin, *J. Amer. Chem. Soc.*, 1947, **69**, 725). Thus the new synthetic route to purines just described appears to be, in outline at least, the method employed in Nature.

Many extensions of these reactions have been or are in the course of being worked out. Alternative syntheses of the pyrimidine ring have been devised by commencing with 5-amino-4 carbamylglyoxalines and inserting the last carbon atom by the agency of carbon disulphide, carbonyl chloride, ethyl orthoformate, and other compounds. Again progress has been made towards introducing sugar groupings, *e.g.*, by means of tetra-acetylglucose *iso*thiocyanate. Time does not permit of detailed discussion of these developments but it is hoped that sufficient has been unfolded to show that α-amino-acids and their near derivatives are, contrary to the view which chemists may sometimes have taken, far from being compounds of rather narrowly limited reactivity and synthetical scope.

Perhaps the simple connections between glycine and other α-amino-acids, glyoxalines, peptides, and purines here outlined may result in quickening interest in these compounds; maybe synthetic purines, which as a class have received such scant attention since the pioneering days of Emil Fischer, will come, with their obvious relations to biologically important compounds, to have an interest as drugs and in other ways comparable with that already attaching to many heterocyclic systems which have hitherto been more readily accessible.

The Goldschmidt Memorial Lecture.

DELIVERED BEFORE THE CHEMICAL SOCIETY ON MAY 20TH, 1948.

By J. D. BERNAL, M.A., F.R.S.

I FEEL very sad at giving this lecture. It was from this very table nineteen years ago at a meeting of the Faraday Society that V. M. Goldschmidt gave his first account in English of the new crystal chemistry that he had done so much to found. That was published in the now historic little book * of the Faraday Society meeting of 1929—and it was there he summed up for us in England the fruit of the extraordinary work that he had been carrying out in the previous few years. It was not new to everyone there; many of us had followed the work in the "Verteilungsgesetz der Elemente," † a series of papers published some two or three years before. These were milestones in crystal chemistry and in general inorganic chemistry, and started a whole train of further work (of which I hardly dare speak here, considering that we have its ablest exponent—Professor Pauling—sitting in the front row). What I will try to do is to show you something, not only of this particular aspect of crystal chemistry, but also of the coherence and unity of the work of Goldschmidt throughout. He combined wide scope and precision in detail in a most exceptional way. He had many ideas but his ideas were not diffuse, they were concentrated on one major problem. In order to deal with something new which arose during a piece of research, he would often make an excursion on one side, but yet always came back to the central problem, which for him was the material constitution of this earth, or more generally of the stellar universe. In doing so he became the founder of modern Geochemistry and of Crystal Chemistry, sciences that will always be associated with his name.

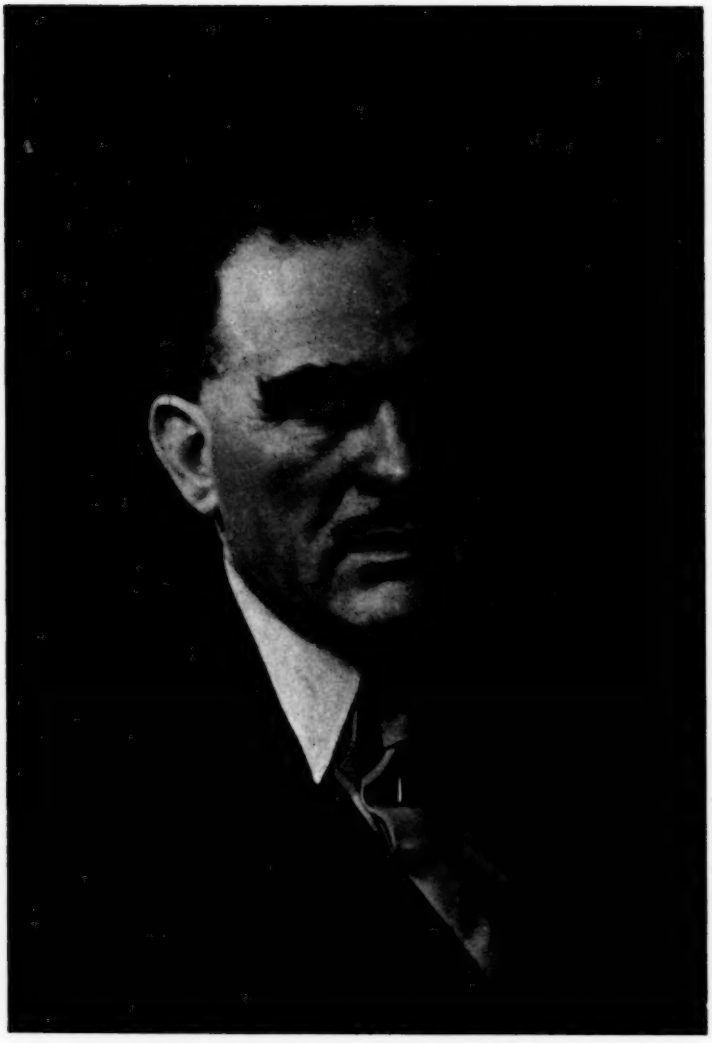
Now the preparation which he had for this task was itself quite exceptional. He was the son of a distinguished chemist, H. Goldschmidt, was born in Zürich in 1888, and was steeped in an intellectual atmosphere from birth. He was, however, not by any means affected only by chemistry. He came very early under the influence of that great Norwegian petrologist and mineralogist, Brøgger, and from him he passed to other masters in various parts of Europe, particularly to Groth's school of crystallography in Munich. He absorbed all that was known there at the time of crystal chemistry. So he returned to Oslo, becoming a Professor at the early age of 26, to start his work essentially as a petrologist. We may divide his work into stages. His petrological period, 1907 to the middle of the first World War, 1916, was followed by a very important intermediate practical period, 1916—1922, in the service of the Norwegian government. Then came the great *X*-ray crystal-chemical period from 1923 to 1927. In 1927 he took up the chair of Mineralogy at Göttingen, combining it with his Oslo chair and travelling between the two by air; but after two years he settled in Göttingen, entered the third period of work, the chemical aspect of the distribution of the elements which he had before treated petrologically and physically, and developed an analytical laboratory of unsurpassed accuracy of determination. On his analytical work alone he would rank as an extremely fine inorganic chemist. He continued it until the first shock of events, which were to have a disastrous effect on his life, forced him out of Germany, where he lost his laboratory and all his apparatus, most of it his own personal property. He went back to Oslo in 1935 where he started all over again. This respite lasted only for a few years, for in 1940 Hitler followed him to Oslo, but even then could not stop him. He worked for the Allies underground, was just not sent to a concentration camp but was imprisoned twice, escaped, literally at the last minute, being sent to the extermination camps of Poland, and finally got to Sweden. Then he came to this country where he spent most of the rest of his life, broken in health, yet able to open a new but final phase of soil geochemistry before his death in March 1947.

The thread of his researches—his intense interest in the elements, their genesis, their affinities and successive associations—was never broken. He would change from one method to another that would promise new and fuller information. Petrology, crystallography, and chemistry themselves, though he enriched all these disciplines markedly, were to him only tools for exploring the world and its history.

Goldschmidt must have very early in his scientific life already laid his plans for this great research. He always gave the impression of a man who knew where he was going, even if it was into the unknown. When I first met him in Bad Ems in 1928 he was recovering from a

* "Crystal Structure and Chemical Constitution," The Faraday Society, March, 1929.

† *Skrifter Norske Vidensk. Akad.*, I., 1923, No. 2; 1924, No. 5; 1925, No. 5; 1926, Nos. 1, 2, 8; 1937, No. 4.



V. M. Goldschmidt

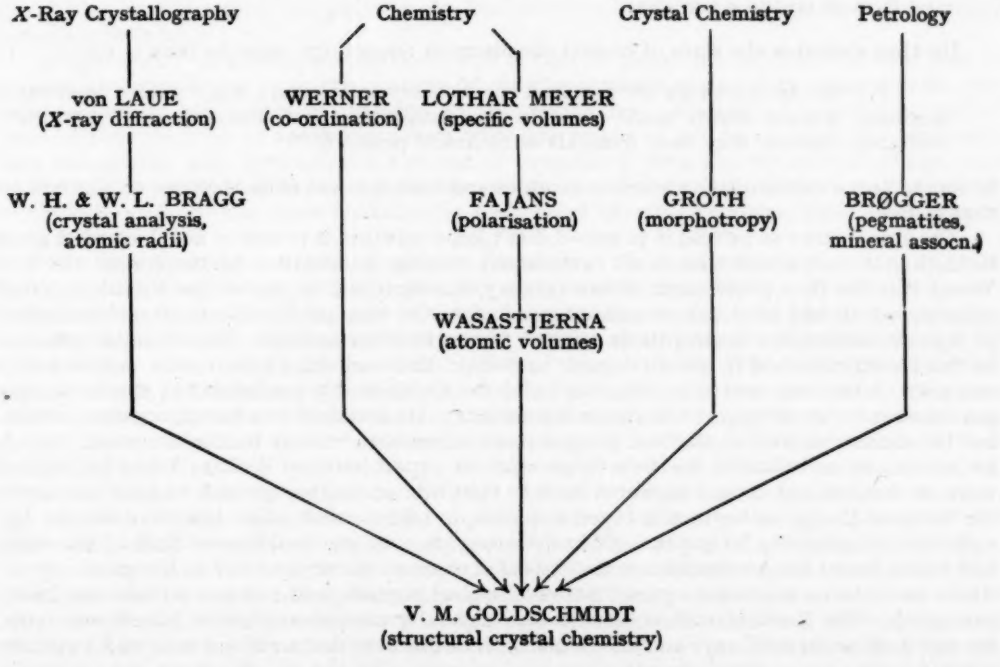
(*Reproduced by courtesy of the Royal Society.*)

[*To face p.* 2108.

bad attack of fluorine poisoning, owing to having been too enthusiastic in watching an analysis. (This may condemn him from the point of view of chemists.) In spite of the fact that he had practically no voice, he spoke of what he wanted to do in geochemistry and what he would actually achieve. An astonishing amount of this he did manage to do in the next 20 years. The sum of his work was going to appear in his great book on Geochemistry, but unfortunately he died just before this was finished; we may yet hope to see this edited, though without the final touch of his master hand.

Here is a great life's work all but complete. To trace how Goldschmidt came to undertake it we have to consider a number of different influences that were acting on him at that period. I have mentioned his law studies; his family and his travels exposed him to nearly all the influences that could lead to a new synthesis of geochemistry and inorganic chemistry. The clue to that synthesis he was to find in *X*-ray crystallography and in the new crystal chemistry which his experience, training, and vision enabled him to found.

Here is another case in the history of science where the genius of a great discovery lies in the ability to effect a junction between widely separated scientific disciplines. It is one of particular interest because, unlike those of Newton or Franklin, Goldschmidt's discovery was based on extensive rather than intensive studies.



The major ideas which he combined are shown in the diagram, but the work of combination was not something to be achieved by any flash of inspiration; it required systematic survey and experiment.

The first work Goldschmidt did was in petrography. He combined an extremely able field geological training with excellent petrographical techniques and a knowledge of physical chemistry, and introduced the latter into his studies of igneous metamorphosis. As a result of his investigations in the Southern Norwegian mountains he developed a reasoned account of changes in igneous rocks, and especially of the pegmatites where the rare elements tended to accumulate. He became particularly interested in the minerals of the rare elements, especially the rare-earth and uranium series, and this interest he never lost. His first paper was on uranium and his last on neptunium and plutonium. He studied the complexes of minerals formed by magmatic differentiation, and was reaching for an analysis of the chemistry that lay behind them. He knew perfectly well the curious laws of replacement and isomorphism which the minerals seemed to have, which did not fit in with the ordinary laws of chemistry, but the new tool, *X*-ray crystallography, which in his hands was to provide a new basis for far

more general laws, only came to him as the result of an altogether external event, the outbreak of the first World War.

Goldschmidt was an intensely practical character, and was concerned to see that his science was used for the benefit of his country. Norway was cut off by German submarines from what had been considered essential supplies. The Norwegian government formed a Materials Supply Committee—and Goldschmidt became its Chairman at the age of 28. It was extremely active and did some remarkable work, particularly in finding local sources for previously imported chemicals. One of these problems was that of extracting potassium from mica, which led him into the very interesting field of the clay mineral studies. This in turn led him to investigate more closely the chemical nature of economic materials, and thus to the study of crystal chemistry. I cannot do better than repeat his own words:

> "The experimental work in the field of crystal chemistry which in recent years the Mineralogical Institute of the University has undertaken had as objective to throw light on the geochemical distribution and technical properties of practically important materials. During the carrying out of these researches which for the most part was by means provided by the Raw Materials Committee of the Norwegian State there appeared a series of generally crystallochemical relationships which made possible a notable deepening of the principles and data of crystal chemistry."

He then describes the state of crystal chemistry in mineralogy when he took it up:

> "For the miner and for the practical chemists crystallography was a purely descriptive auxiliary science which made possible the recognition and distinction of crystalline materials whether they were minerals or technical products."

It was in fact a determinative science, much as spectroscopy was from the time of Kirchoff to that of Bohr.

The actual story as he told it to me—I don't know whether it is true or not, but it is a good Goldschmidt story—was that it all came about through a lawsuit. At the end of the first World War the then government of this country, feeling it had to protect the British chemical industry which had been left so undeveloped before the war, produced a tariff on the import of organic chemicals. Among those referred to was calcium carbide. The chemical interests in this country claimed it was an organic chemical; the Norwegian government maintained it was not. A test case was to be fought in London. Goldschmidt was briefed by the Norwegian government to be the expert witness on the subject. He certainly was not an organic chemist, but he read a text-book on the boat going across and set forth bravely for the law court. When he learned on arrival that the British government expert was Sir William Pope, he decided after all it would not do and he would have to fight him on another ground. Luckily he knew Sir William Bragg, so he took a crystal of calcium carbide and asked him to work out the structure (incidentally he got it completely wrong, but no one could know that at the time) and Goldschmidt fought the case on the basis that this was the structure of an inorganic crystal. There could be no argument against this on chemical grounds, and calcium carbide was finally exempted. The Norwegian Government were naturally pleased and asked how it was done. He put it all down to *X*-rays and on the strength of this obtained an *X*-ray tube and a powder camera.

He wanted to start work straight away, but, realising that with his limited knowledge and apparatus he could not compete with the Braggs in the analysis of complex minerals like the silicates, he began on simple structures—the AX and AX_2 compounds which were mostly of the rock salt, cæsium chloride, rutile, corundum, and calcium fluoride types. The structures of all these were already known. Goldschmidt's original approach was to examine systematically binary compounds of most of the elements. What he did was a model of extensive work. In that sense he was a real chemist; a physicist would spend years working out one structure, but he spent a few months working out a very large number. In two years he and his co-workers, several of whom like Barth, Oftedal, and Zachariasen were to become noted geochemists and crystallographers, worked out structures of 200 compounds of 75 elements and in that way established the extensive basis on which to found general laws.

The sequence of the work is rather interesting. He started on the uranium compounds, with which he was already familiar, to get his hand in. Then he went on to another set of compounds, also of geochemical interest, the rare earth sesquioxides (A_2X_3 compounds). The significance of this choice, probably a deliberate one, was that it was here he began to make

comparative studies of compounds of the same type of formula, $A_xB_yC_z$ . . . and not as he and others had done before, either of compounds of a limited group of chemical elements or of one of isomorphous compounds. He had here the advantage of possessing a unique and almost complete collection of rare earths. He showed that the sesquioxides occurred in three overlapping structures which he called A, B, and C. $_{51}$La showed A only, $_{58}$Ce to $_{60}$Nd A and B, $_{61}$Sm alone A, B and C, $_{62}$Eu to $_{66}$Dy B and C, and $_{67}$Ho to $_{71}$Lu only C. The reason for these transitions could not be chemical, it must depend on some physical property. Goldschmidt had the genius to seize on the simplest of these, the size of the atoms, guided by the clue of the small but steady diminution of the lattice parameters in going towards the higher atomic numbers, the celebrated lanthanide contraction.

At that time arguments about atomic sizes were hopelessly confused owing to a quite natural misreading of the meaning of the Lothar-Meyer curve. Specific volumes had been identified with atomic and even with ionic volumes and, as the largest specific volumes were associated with metals, it was assumed that the metal ions were the largest. Early *X*-ray work had apparently substantiated this view as it was possible to account for the lattice dimensions of the alkali halides by assuming large cations and small anions. Already, however, doubts about this view had arisen because it failed to explain the high polarisability of the anions. Fajans and after him Wasastjerna demonstrated on these grounds that the properties of ions could best be understood by reversing the accepted procedure and making the cations small and the anions large.

Goldschmidt's characteristic contribution was that of using this new view of ionic size to explain the morphotropy, or the changes of structure, which occurred in passing along any series of similar compounds on changing the atomic number. He noticed that this transition from one crystal type to another occurred when the radius of one or other of its constituent ions was altered, and, by considering groups of compounds with ions of different charge such as the halides and the oxides, that it was the radius ratio that determined the structure. This led him directly to the most fundamental concept of crystal chemistry, the importance of co-ordination.

Now co-ordination was nothing new in chemistry. It had been introduced by Werner fifty years before to account for the peculiarities of the ions of complex salts. What Goldschmidt did was to point to its crucial role in determining the structure of the simplest crystalline compounds. In spite of the enormously wide variety of crystal structures known even in the inorganic sphere, the varieties of co-ordination are absolutely limited and are derivable from the simplest geometrical considerations. Goldschmidt took the small positive cations as the co-ordinating ions. As they increased in size relatively to the large negative non-metallic anions the co-ordination number increased: beginning with two in a line, passing on to three in a triangle, to four in a tetrahedron, to six in an octahedron, and finally to eight in a cube. The cube marked the turning point. A larger ratio, implying a cation larger than an anion, led to inverted structures. Goldschmidt applied and tested this rule on most of the structures of the simple ionic compounds, those of the types AX, AX_2, A_2X_3, ABX_3, A_2BX_3, and A_2BX_4.

It was at about this period that he moved to Göttingen and renewed his contact with Max Born who was then elaborating the precise quantitative theory of the lattice energy of simple ionic compounds. Goldschmidt's work was complementary to that of Born, the one following the line of intensive study, the other of extensive exploration. Once he had realised that the physical basis for the simple crystallochemical laws lay in the electrostatic attraction between ions of different signs and different sizes, he was able to go further and search for the limits of the applicability of these laws. These, he found, in two different directions, one that of the polarisability of the anions and the other that of the non-electrostatic character of the interatomic bond. He was able to show that the structures of the sulphides and some of the higher halides of small, highly charged, and consequently highly polarising cations, were not of a fully ionic character, for although the anions were co-ordinated round the cations in a normal manner the reverse was not the case. The anions were so polarised by the cations that they had become dipoles on their own account and that structure was composed of rods or sheets held together by relatively weak dipole and van der Waals forces. It was from this that he was able to evolve the first general law of crystal chemistry, his law that *the structure of a crystal is determined by the numerical proportions, the ratio of radii, and the polarisability of its ions.*

The other exception was to be found in the neighbourhood of the fourth column of the periodic table, compounds such as zinc selenide, gallium arsenide, or germanium metal, where the interatomic distance hardly varied with the type of compound, and where simple additive laws no longer held. These compounds Goldschmidt talked of as being commensurable with

ionic compounds. They are, in fact, the group that we now recognise as being held together by covalent bonds, making the whole structure a gigantic molecule, in the semi-metallic or adamantine compounds whose electronic and particularly whose semi-conducting properties are now receiving so much attention. These non-ionic compounds he recognised as incommensurable with the ionic compounds and intermediate between them and the metals.

As the result of his extensive studies on ionic compounds Goldschmidt was able to draw up the first tables of empirical atomic radii for most of the ions in the periodic table. He was thus able to understand clearly for the first time the significance of the replacement laws that had made mineralogical chemistry such a confusing subject. The extremely complex formulæ of such minerals as tourmaline and mica, for example, he showed to be due to the apparent indifference of any crystal structure to the particular character or even to the charge of its constituent ions if the total charges of positive and negative ions were balanced. He had earlier shown, by studying the isomorphism of calcium difluoride and yttrium trifluoride, that this balance could be achieved by simply leaving out a certain number of ions from their possible positions in the structure, thus opening the field to the concepts of defect structures. This observation is of the most fundamental importance to the whole theory of chemistry, because it shows that the laws of constant and multiple proportions of Dalton apply strictly only for covalent compounds, that is, for molecular compounds. The reason they appear to hold for ionic compounds or salts is simply that of the equivalence of positive and negative charges, and they lose all meaning in the case of metallic compounds. Goldschmidt did not confine himself to the explanation of the actual structure of the ionic crystals. He was also concerned with their physical properties. He showed in particular how the characteristic hardness of the minerals is associated with the relative charges and interatomic distances of the compounds, and he introduced the extremely ingenious idea of model substances, that is, of substances with the same radii of positive and negative ions but with half the charges. Beryllium fluoride is in this way a model for quartz, and rubidium borofluoride for barium sulphate, compounds resembling each other crystallographically but differing in their melting points and hardness.

It was at this point that the work of Goldschmidt merged into the far more detailed analysis of ionic compounds which was being carried out particularly by the school of Sir Lawrence Bragg in Manchester. The structures of the silicates, far more complex than any that Goldschmidt had attacked, were being determined by precise and absolute physical methods. As the results of one structure after another came out, the fundamental difference, recognised in an empirical way by the mineralogical chemists, between the acid and the basic silicates began to appear, the latter containing isolated SiO_4 ions and these polymerising into rings, chains, and sheets as the ultimate limit of pure crystalline silica itself was reached. Working in Bragg's laboratory, Pauling was able to combine this new knowledge with Goldschmidt's generalisation, to provide the first explicit series of laws of ionic crystal chemistry, the celebrated Pauling Rules, which enabled the possible types of crystal structure to be deduced from the knowledge of the relative numbers, charges, and sizes of the constituent ions. The works of Goldschmidt, Bragg, and Pauling are therefore inextricably combined in this foundation of modern inorganic chemistry.

Before leaving this field, however, Goldschmidt entered the last remaining large area of chemical ignorance, that of the metals and alloys. Here he early realised that the effective diameters of atoms were quite different from those in the ionic state and were always larger. The differences varied very much between the alkali metals, where they were more than twice, and the transition metals, where they were hardly anything at all. He was able to draw up the first table of metallic radii and was even able to make allowance for the different effects of co-ordination by persuading atoms which are normally of fairly low co-ordination, such as bismuth (6), to show twelve-fold co-ordination by alloying them with others such as silver in which this is the natural co-ordination and observing the proportionate charge in parameter. As Hume Rothery showed, the atomic size is not the only determinant of alloy structure; where these do not differ much, the ratio of electrons to atoms is as important. Nevertheless the work of Goldschmidt marks him here also as one of the founders of modern alloy chemistry.

After his brilliant and now historic excursion into the field of crystal chemistry, Goldschmidt in 1928 returned to his first and lifelong interest, that of geochemistry. He had at the outset set himself the problem of how the elements are distributed in the crust of the earth. This was the "Verteilungsgesetz der Elemente," those classical monographs in which he summed up the major part of his life's work. He had found in crystal chemistry the clue to this distribution as determined by the size, charge, and polarisability of the respective ions they formed. He saw that the very nature of the spheres into which the earth was divided was determined

by the ionic character of the major elements, those of oxygen, silicon, iron, and magnesium. The core, he thought, was made of iron in which a number of elements such as platinum and siderophilic elements were dissolved. Next to that he postulated an intermediate layer containing the elements allied to sulphur, arsenic, etc., the so-called chalcophilic elements such as lead and copper.

These inner layers of the earth must always remain somewhat hypothetical, but Goldschmidt was on much safer ground in coming to the next main sphere of the earth's interior, the lithosphere. The lithophilic elements are predominantly the silicates of iron, magnesium, calcium, aluminium, and the alkalis, in that order passing upwards. The density of a rock and consequently its height from the earth's centre will depend on the degree of effective packing of its ions rather than on the specific gravity of the ions themselves; thus uranium, though a very heavy ion, forms, on account of its large size, silicates which are relatively light and thus is found in the more acid and higher rocks. Goldschmidt was particularly interested in the distribution of the rare elements, not on any pedantic grounds but because he used them consciously as tracers for the physical and chemical reactions that went on in rock formation and metamorphosis. It was for this purpose that he established at Göttingen the analytical laboratory in which he analysed thousands of rock and mineral specimens and developed new analytical methods of great refinement. I remember his telling me that it was necessary to remove any jewellery from visitors to his laboratory for fear they would contaminate his gold and silver analyses.

Anaylsis was however for him only a means to an end. He was really concerned with the logic of the interchange of elements; as he liked to put it himself, he felt himself in charge of the account-books of the universe. One fascinating piece of research which he carried out was that by which he found the concentrations of germanium in the ash from certain kinds of Newcastle coal.* The argument was briefly this: in a forest, the roots of the trees draw up with the water the elements contained in solution at very high dilution as salts. These pass to the leaves where most of the water is evaporated. Consequently the leaves at the end of the season contain a relatively high proportion of a large number of elements. The leaves fall to the ground and in a well-established or primitive forest the soil to a considerable depth is formed entirely of them. They in turn are subject to leaching, which removes the majority of soluble salts. The result is the gradual accumulation of the insoluble salts of very rare metals often in toxic strength. He made analyses of the soil of some very old forests and showed, for instance, that some of them contained enough arsenic to prevent the effective growth of anything with shallow roots between the trees. Ultimately the forest bed is conyerted into coal, but the rare elements and particularly the germanium remain in it.

Another example of his powers of interpretation was provided in the case of certain nodules found very generally in red sandstone. Very fine examples of these were collected by Mr. G. E. L. Carter from Budleigh Salterton, and were shown by him to be radioactive. Dr. Perutz † in my laboratory studied these in detail and found they consisted almost entirely of vanadium salts with isolated crystals of uranium salts. Goldschmidt explained their occurrence as follows: all iron-bearing rocks contain a small amount of tervalent vanadium replacing iron. Under conditions of extreme oxidation such as occur in deserts, some of this vanadium is oxidised to the quinquevalent state. In this state it is soluble and washes down into the clay pans which are found dispersed in all desert formations. Here the vanadium salts are concentrated by biological action into concretions which are ultimately consolidated and recrystallised by metamorphic action.

Goldschmidt must rank after Vernadsky as the founder of modern geochemistry. Not only did he establish an enormous amount of factual data in geochemistry, but he also gave all geochemical problems that he touched a rational interpretation in terms of crystal chemistry and ultimately of physics.

It was at this stage that Goldschmidt's work was first seriously interrupted by political events. The advent of Hitler forced him to leave his great laboratory at Göttingen with all the apparatus most of which he had purchased with his private fortune. He was, however, with indomitable energy, able to reconstruct it at Oslo and there, for the last hectic years before the war, continue his work. The war saw him in hiding, arrested, in prison, escaping, and finally reaching Britain. Here at the Macaulay Institute and at Rothamsted he started a field of study which, if he had lived, would have equalled that of the others in importance. This was the application of geochemical methods to soil science or, as he would put it, the chemistry of the biosphere.

* Coal Research (B.C.U.R.A.), London, June 1944. † *Min. Petr. Mitt.*, 1939, **51**, 141.

He was, however, already broken in health and hardly survived by a year his return to Norway.

With Goldschmidt there died a great man as well as a great scientist. He was a man of extraordinary courage and self-sufficiency. He was solitary but was extremely friendly and sympathetic to others. He possessed an enormous fund of intellectual energy and a determination which carried him through to the end of his comprehensive scientific projects. He was at his best in adversity and was never defeated by all the hard blows which fate served out to him. I remember his telling me after his first expulsion from Germany how thankful he was to Hitler. " If it had not been for Hitler," he said, " I should have remained a Geheimrat Professor at Göttingen, more and more honoured and more and more bored. Now I am an exile, I have no laboratory, no position, no money, and so life is starting all over again, more exciting than ever, and," he added, " I have found out how really good people are. In ordinary life you can never find whether people are genuinely good, because it pays to be good. Under Hitler, everything is reversed. It pays to be as nasty as possible, and it is surprising, in spite of that, how many good people I have found—even among the educated classes." Another typical story of him is of the days just after Hitler's coming to power when he arrived in the Senate of the University with his short hair cut even more closely than ever. When he was asked why, he answered, " Damit es besser rollen kann," for Hitler had always promised that " heads must roll." But Goldschmidt outlived Hitler and outdid him. All through the early part of the war he used his abilities to deceive the Nazis as to the mineral resources of his country, leading them to waste enormous efforts where there was nothing useful to be found. At first with characteristic stupidity, they failed to recognise his existence at all. When he was had up before the Gestapo and accused of having been dismissed from the Professorship at Göttingen, he asserted he had resigned and produced in proof a certificate to that effect signed by Goering as Minister of Education and Hitler as Vice-Chancellor; the Gestapo official said that it was a forgery; Goldschmidt answered, " That may be so, but when I receive documents signed by the heads of the German state I cannot assume that they are forgeries." For this sally he received two months' imprisonment. But his real crime, of being a Jew, was not then discovered. He was fortunate at the last moment to avoid deportation to Poland and a death camp. Instead he escaped, hid in the woods, and finally found his way to Sweden where, he said, he was delighted to find that at last he was among people who knew who he was.

Goldschmidt was, indeed, one of the really great men of science, one with that rare combination of comprehensive grasp of a complex subject and deep penetration which revealed its underlying structure. We know already that his work will last, that it has taken its place in the permanent structure of science. His work in geochemistry and crystal chemistry would each by themselves suffice to give him an outstanding place in the history of science, to say nothing of his contribution to petrology, of which I am not competent to speak, but which was of the highest order. It is to Goldschmidt more than to anyone else that we owe the picture of atoms and ions of definite measurable sizes, and of their combination at least in organic and metal chemistry as a function of their size. In a few years' time, Goldschmidt's crystal chemistry will take a place beside, if it does not replace, the work of Lavoisier in the merit of not being merely true, but also extremely simple and beautiful. His work on geochemistry cannot expect to have the same finality, but here again the concepts of atomic radii and co-ordination will provide a clue for the complex transformations that have accounted for the history of the earth on which we live.

Chemistry and Biochemistry of Some Mammalian Secretions and Excretions.

A CENTENARY LECTURE DELIVERED BEFORE THE CHEMICAL SOCIETY AT THE ROYAL INSTITUTION ON MAY 12TH, 1949.

By EDGAR LEDERER,* D.Phil., D.-ès.-Sc.

DURING the last nine years we have studied in detail the chemical composition of different animal secretions and excretions. The result of this work seems to present a certain interest, not only from the point of view of the particular drug or material studied, but also from a larger, biochemical point of view. We have isolated a certain number of new substances, the constitutions of which were determined whenever possible; we have tried to find satisfactory biochemical explanations for the presence or formation of these substances in the animal. The following materials were studied: (1) the scent gland of the beaver; (2) pregnant mare's urine; (3) wool fat; and (4) ambergris.

(1) THE SCENT GLAND OF THE BEVER (CASTOREUM).

The dried scent glands of the Canadian beaver (*Castor fiber*) are commercially known under the name castoreum and are still utilized in perfumery because of the strong animal odour of their extracts. The beaver of either sex has two of these pearshaped organs in the anal region, which weigh about 25—50 g. each. Their secretion is voided into the cloaca, and the beaver is said to leave an odorous trail which allows the animals to find one another.

The only papers on the chemical composition of the scent glands of the beaver were those of Walbaum and Rosenthal (*J. pr. Chem.*, **1927**, **117**, 225) and of Pfau (*Perf. and Ess. Oil Rec.*, **1927**, **18**, 206) describing the isolation of benzyl alcohol, borneol, *p*-ethylphenol, acetophenone, benzoic and salicylic acids. We have confirmed all these findings and have isolated about forty other substances, some of which have never before been found in Nature, others which have never been described at all; still others are awaiting isolation and identification.

Table I lists about forty of these compounds. It is certainly very astonishing to find so many unusual, mostly aromatic substances in an animal gland. In the course of our work we

TABLE I.

Constituents of castoreum (scent glands of the Canadian beaver).

Alcohols:	benzyl alcohol (free and esterified), cholesterol, β-cholestanol, mannitol (*U*), *cis*-5-hydroxytetrahydroionol (*U*).
Phenols:	*p*-ethylphenol (*U*, *b*), *p*-propylphenol (*b*), pyrocatechol (*U*), quinol (*U*), quinol monomethyl ether (*a*), chavicol (*a*), 2-hydroxy-5-ethylanisole (*a*), 4-methyl- (*a*) and 4-ethyl-pyrocatechol (*a*), betuligenol (*a*), 2 : 4′-dihydroxydiphenylmethane (*b*), 2′ : 3″-dihydroxydibenz-2-pyrone (pigment I, *c*), 4 : 4′-dihydroxydiphenic acid dilactone (pigment II, *c*); a phenolic ether, m. p. 83° (*c*).
Aldehydes:	salicylaldehyde (*a*).
Ketones:	acetophenone (*a*), *p*-hydroxyacetophenone (*a*), *p*-methoxyacetophenone (*b*), aromatic ketone $C_{10}H_{12}O_2$, two isomeric hydroxy-ketones $C_{13}H_{24}O_2$ probably derived from ionone (*U*, *b*).
Acids:	benzoic (*U*), β-phenylpropionic (*a*), cinnamic (*U*), salicylic (*U*), *m*-hydroxybenzoic (*U*), *p*-hydroxybenzoic (*U*), anisic (*a*), gentisic (*U*), 5-methoxysalicylic (*b*).
Esters:	cholesterol oleate, a phenolic ester (m. p. 170°), esters of ceryl and benzyl alcohol, and of phenols and gentisic acid.
Amines:	castoramine, $C_{13}H_{23}O_2N$, m. p. 66° (*c*).

(*U*), Normally found in urine. (*a*) Isolated for the first time from an animal organ.
(*b*) Isolated for the first time from a natural source. (*c*) New compound.

came to the conclusion that two main reasons explain this. First, the special food habits of the beaver: his food consists mainly of buds and barks of trees; these plant tissues contain a great number of substances which we have found also in the scent glands (borneol, pyrocatechol, betuligenol, *p*-hydroxyacetophenone, salicylaldehyde, benzoic, cinnamic, and salicylic acids, etc.). In other vertebrates, such substances, ingested with the food, would be excreted in the urine after appropriate conjugation. The *beaver*, on the contrary, *deposits these in his scent*

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glands, without conjugation; this is the second reason which explains the extraordinary composition of this secretion. The numerous substances of Table I, marked (*U*) are those which are normal constituents of vertebrate urine.

Some substances are deposited unchanged, some after hydrolysis of the glycosidic linkage (piceoside ⟶ *p*-hydroxyacetophenone; betuloside ⟶ betuligenol), others after oxidation (salicylic acid ⟶ gentisic acid) or reduction (xanthophylls ⟶ tetrahydroionones; cinnamic acid ⟶ β-phenylpropionic acid).

We shall next discuss in greater detail the chemistry and biochemistry of some of the constituents of castoreum.

Mannitol. In a recent note on the constituents of castoreum (*Nature*, 1946, **157**, 231) we mentioned a " water-soluble nitrogen-free substance melting at 173°." We have since identified it as D-mannitol, which is a normal constituent of dog's urine (Kapfhammer and Prell, *Biochem. J.*, 1937, **295**, 91) but seems not to have been found before in an animal organ.

Acetophenone. The presence of rather large amounts of this ketone, which is found only in very small amounts in some essential oils, can be explained by a mechanism described by Dakin (*J. Biol. Chem.*, 1909, **6**, 217; **9**, 123) in experiments involving administration of β-phenylpropionic acid to cats and dogs; this acid is oxidized at the β-carbon and then decarboxylated to acetophenone, which was found in the urine.

$$Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H \longrightarrow OH{\cdot}CHPh{\cdot}CH_2{\cdot}CO_2H \longrightarrow Ph{\cdot}CO{\cdot}CH_2{\cdot}CO_2H \longrightarrow Ph{\cdot}CO{\cdot}CH_3$$

Gentisic acid, which is one of the major acids of castoreum, is the normal oxidation product of salicylic acid in the vertebrates and is usually found in the urine after administration of salicylic acid (Kapp and Coburn, *J. Biol. Chem.*, 1942, **145**, 549; Lutwak-Mann, *Biochem. J.*, 1943, **37**, 246). However, it had not previously been found in an animal tissue.

Betuligenol is a phenol, $C_{10}H_{14}O_2$, m. p. 80°, the constitution of which we established in 1941, independently of Sosa (*Ann. Chim.*, 1940, **11**, 1) who had isolated it as an aglycone of betuloside extracted from the bark of the birch. Oxidation of the monomethyl ether of betuligenol with permanganate gave anisic acid, and chromic acid oxidation gave 1-*p*-methoxyphenylbutan-3-one, identical with the synthetic product. Betuligenol must thus be 1-*p*-hydroxyphenylbutan-3-ol, one of the rare natural aromatic substances with a butyl side chain (Lederer and Polonsky, *Bull. Soc. Chim. biol.*, 1942, **24**, 1386).

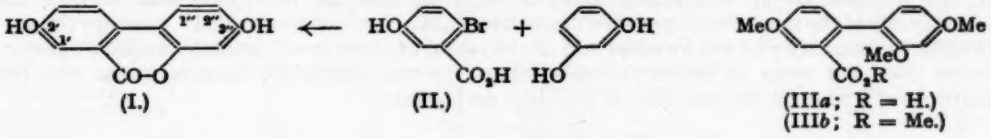
2 : 4′-*Dihydroxydiphenylmethane*, m. p. 120°, was identified by chromic acid oxidation to 2 : 4′-dihydroxybenzophenone. This is the first time that this substance has been isolated from a natural source.

Pigments of castoreum. The scent glands of the beaver contain two new yellow pigments; they are soluble with an intense yellow colour in aqueous carbonate and can be separated from one another by fractional crystallisation of their colourless acetates (Lederer, *ibid.*, p. 1155).

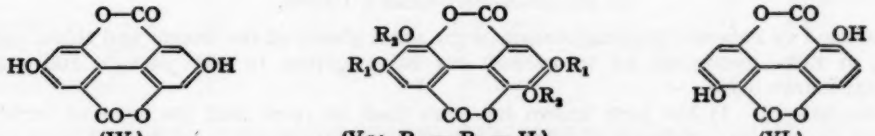
Pigment I, $C_{13}H_8O_4$, can be obtained as yellow needles, melting above 360° (decomp.), by hydrolysis of its diacetate, m. p. 210°. It contains two phenolic hydroxyls and one lactone group. By distillation with zinc powder it is reduced to fluorene, $C_{13}H_{10}$, whereby all 13 carbon atoms are accounted for. Fusion with potassium hydroxide gives *m*-hydroxybenzoic acid. These results, as well as the positive Griessmayer reaction (see below), led us to formulate pigment I as 2′ : 3″-dihydroxydibenzo-2-pyrone (I). We have recently confirmed this structure by synthesis, using the method of Hurtley (*J.*, 1929, 1870). By condensing 2-bromo-5-hydroxybenzoic acid (II) with resorcinol, in the presence of traces of copper sulphate as catalyst, we have obtained a yellow pigment, the diacetate, the dimethyl ether, and the two derivatives (III*a*) and (III*b*), none of which depressed the melting points of the natural derivatives (Lederer and Polonsky, *Bull. Soc. chim.*, 1948, 831). The same method may be used to synthesize various analogues of pigment I.

Pigment II of castoreum is obtained by hydrolysis of its very insoluble diacetate, m. p. 320°. It forms greenish-yellow needles, which do not melt at 360°. Its formula is $C_{14}H_6O_6$ and it contains two phenolic hydroxyl groups and two lactone groups, whereby all six oxygen atoms are accounted for. On distillation with zinc powder, it is also reduced to fluorene, and fusion with potassium hydroxide gives β-resorcylic acid. These results lead to the formula (IV) for this pigment (Lederer, *Bull. Soc. Chim. biol.*, 1942, **24**, 1155). An asymmetrical formula, with only one hydroxyl in a 4-position of the diphenyl group, would however still be compatible with the above-mentioned experimental results. We excluded this possibility by studying Griessmayer's reaction (*Annalen*, 1871, **160**, 51) with similar pigments. This reaction consists in heating ellagic acid (V*a*) or similar pigments with nitrous acid containing nitric acid, whereupon a red colour develops which is stable after dilution with water. We found that only those

pigments which contain at least two free hydroxyl groups in 4 : 4′-positions of the diphenyl nucleus give this reaction. This rule was also found true for the synthetic dibenz-2-pyrones.



(I.) (II.) (IIIa; R = H.) (IIIb; R = Me.)



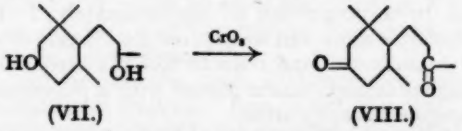
(IV.) (Va; $R_1 = R_2 = H$.) (Vb; $R_1 = H$; $R_2 = Me$.) (Vc; $R_1 = Me$; $R_2 = H$.) (VI.)

Shinoda and Kun (*J. Pharm. Soc. Japan*, 1931, **51**, 50) have described a dimethyl ether of ellagic acid, m. p. 337°, isolated from the roots of *Euphorbia formosana*, which gives no reaction with ferric chloride but gives a positive Griessmayer reaction. This must therefore be (V*b*), and the isomeric dimethyl ether which Goldschmiedt (*Monatsh.*, 1905, **26**, 1139) prepared by methylation of ellagic acid must be (V*c*).

In the course of this work we became interested in an isomer of pigment II, obtained by Juch (*Monatsh.*, 1905, **26**, 839) by oxidation of gentisic acid with manganese dioxide. The exact structure of this pigment had not been established, but Juch stated that distillation with zinc dust reduced it to phenanthrene (m.p. 100°). On repeating his experiment, we found that his phenanthrene was in reality fluorene (m. p. 116°), and therefore his pigment must have the structure (VI); the Griessmayer reaction of this pigment is of course negative.

Pigment I and, more so, pigment II have a close relation with ellagic acid (V*a*), which is abundant in the bark of trees. It is as yet difficult to tell if these two pigments of castoreum are reduction products of ellagic acid, or if they exist as such in some plant material.

Derivatives of ionone. Prelog and collaborators (*Helv. Chim. Acta*, 1947, **30**, 113; 1948, **31**, 1799) have recently described the isolation and synthesis of a series of very interesting neutral substances with thirteen carbon atoms, isolated from pregnant-mare's urine. These are glycols



(VII.) (VIII.)

(VII), keto-alcohols, and diketones (VIII) derived from tetrahydroionone and having one of the oxygen atoms in the same position as the carbonyl group of ionone and the second oxygen atom on the ring-carbon atom 5, that is, the carbon atom at which the xanthophylls have their hydroxyl group. Prelog and his collaborators think that these substances are derived from the xanthophyll pigments of the food.

In 1943, we described an amorphous glycol, isolated from castoreum (*Bull. Soc. Chim. biol.*, 1943, **25**, 1381) for which we had proposed the formula $C_{12}H_{24}O_2$ of a monocyclic glycol; the oxidation of this glycol had given a diketone (bis-2 : 4-dinitrophenylhydrazone, m. p. 198°) showing the characteristic colour reaction of methyl ketones. Since then, our glycol has crystallized (m. p. 100°) and a later conversation with Professor Prelog bore out the probability that our glycol was identical with the mixture (m. p. 103°) of stereoisomeric diols $C_{13}H_{26}O_2$ isolated in Zürich from pregnant-mare's urine. A comparison of the bisphenylsemicarbazones and the bis-2 : 4-dinitrophenylhydrazones, and of the infra-red spectra of our diketone with that of Prelog's compound confirmed the identity (Lederer, Prelog, and Schneider, *Helv. Chim. Acta*, 1948, **31**, 2133). It is very probable that the two isomeric keto-alcohols $C_{13}H_{24}O_2$ which we had also isolated from castoreum (*Bull. Soc. Chim. biol.*, 1943, **25**, 1073) are identical with corresponding ionone derivatives isolated by Prelog *et al.* We have here a new illustration of the parallelism between castoreum and the urine of vertebrates, and a strong indication that the ionone derivatives of Prelog *et al.* are of general importance as degradation products of carotenoids.

Castoramine is a crystalline base, m. p. 66°, isolated from castoreum (*ibid.*, p. 1299); it has

the formula $C_{15}H_{23}O_2N$ and is characterised by its sparingly soluble sulphate, m. p. 216°. Castoramine contains no methoxyl or methylimide group and no mobile hydrogen. Recently Schinz, Ruzicka, Geyer, and Prelog (*Helv. Chim. Acta*, 1946, **29**, 1524) have isolated from the musk glands of the musk deer a pyridine derivative $C_{16}H_{25}N$, which they called " muscopyridine." Despite the similarity of the formulæ and of the origin of these two " animal alkaloids," castoramine does not seem to be very closely related to muscopyridine, because it has not the characteristic absorption spectrum of pyridine derivatives.*

(2) Pregnant-mare's Urine.

The analogy between the constituents of the scent glands of the beaver and those normally found in urine prompted us to extend our investigation to the phenols and acids of pregnant-mare's urine.

p-*Ethylphenol*. It has been known for more than 50 years that the urine of vertebrates contains the ethereal sulphates of different phenolic substances which are derived from tyrosine by bacterial degradation in the intestine. Baumann had already in 1879 (*Ber.*, 1879, **12**, 1452) proposed the following scheme of degradation of tyrosine: tyrosine ⟶ *p*-hydroxyphenylpropionic acid ⟶ *p*-ethylphenol ⟶ *p*-hydroxyphenylacetic acid ⟶ *p*-cresol ⟶ *p*-hydroxybenzoic acid ⟶ phenol. All these substances had since been isolated from urine of vertebrates, except one, *p*-ethylphenol.

Having confirmed the findings of Walbaum and Rosenthal (*loc. cit.*) and of Pfau (*loc. cit.*) that *p*-ethylphenol is the principal phenol of castoreum and having established the close relation between the constituents of this animal gland and the substances normally excreted by other vertebrates in the urine, we thought that *p*-ethylphenol should also be a normal constituent of vertebrate urine. By a careful fractional distillation of the phenolic non-ketonic portion of an extract of hydrolysed pregnant-mare's urine, we were able to isolate a phenol, the phenylurethane and glycollic acid ether of which did not depress the melting points of derivatives of authentic *p*-ethylphenol (*ibid.*, p. 1237). In pregnant-mare's urine, *p*-ethylphenol amounts only to 4—10% of the *p*-cresol present. In castoreum, on the contrary, we have found no *p*-cresol at all. That there actually exist very definite species differences between the phenols excreted in the urine of different vertebrates is shown by the recent report of Grant (*Biochem. J.*, 1948, **43**, 523) who isolated the ethereal sulphate of *p*-ethylphenol from goat's urine and found *p*-cresol to be present in only very small amounts. Thus castoreum seems to resemble goat's urine closely in this respect.

p-*Propylphenol* had never been isolated from an animal or plant tissue; in castoreum it accompanies *p*-ethylphenol in a proportion of approximately 1 : 10. We have found no *p*-propylphenol in pregnant-mare's urine, but we suppose that it may also be derived in the beaver from tyrosine by bacterial deamination and reduction of the carboxyl group. It is significant that no *p*-butylphenol or higher straight-chain phenol with a *p*-hydroxyl group has been found either in castoreum or in pregnant-mare's urine.

Acids. The presence of *m*-hydroxybenzoic acid in castoreum had surprised us; this acid had only once before been isolated from a natural source. Bielig and Hayasida (*Z. physiol. Chem.*, 1940, **266**, 99) found it in the urine of rabbits which had been dosed with β-ionone. They recognized, of course, that the β-ionone could not have been transformed into *m*-hydroxybenzoic acid, but they did not suspect that it could be a normal constituent of vertebrate's urine.

The numerous analogies, already cited, between the constituents of the scent gland of the beaver and vertebrate's urine led us to suppose that *m*-hydroxybenzoic acid was, in fact, a normal constituent of vertebrate's urine; so we decided to analyse the acids of pregnant-mare's urine which are industrial by-products of the production of the female sex hormones. This study seemed all the more interesting as no such analysis had yet been made in detail.

By fractional distillation of the ethyl esters of 900 g. of acids of pregnant-mare's urine we have isolated fifteen acids (see Table II), thirteen of which have been identified; only four of these had been known until then as normal constituents of vertebrate's urine: benzoic, phenylacetic, *p*-hydroxybenzoic, and azelaic acid (Lederer and Polonsky, *Biochim. Biophys. Acta*, 1948, **2**, 431). The nine new acids are salicylic, vanillic, *m*-hydroxybenzoic (which thus *is* actually a normal constituent of urine), three unsaturated acids [cinnamic, *p*-cumaric (*p*-hydroxycinnamic), and ferulic (4-hydroxy-3-methoxycinnamic) acid], and three acids which had not yet been isolated from a natural source [*m*-methoxybenzoic, dihydroferulic (4-hydroxy-3-methoxyphenylpropionic acid) and decane-1 : 10-dicarboxylic acid] (see Table II).

* We have to thank Professor V. Prelog for measuring the absorption spectrum of castoramine.

TABLE II.

Acids isolated from pregnant-mare's urine.

Acid.	M. p.	% of total acid.	Mg. per l. of urine.	Acid.	M. p.	% of total acid.	Mg. per l. of urine.
Benzoic	122°	74	2460	Substituted salicylic (not identified)	118°	0·07	2·3
Phenylacetic	76	14	460	Ferulic	170	0·04	1·3
p-Hydroxybenzoic	214	1·3	43	Vanillic	205	0·03	0·9
Salicylic	156	0·7	23	*m*-Methoxybenzoic	105	0·025	0·7
Azelaic	107	0·4	13	Cinnamic	134	0·02	0·6
Dihydroferulic	90	0·2	6·6	Phenolic (not identified)	208	0·01	0·3
Decane-1 : 10-dicarboxylic	128	0·1	3·3	*p*-Cumaric	210	0·002	0·06
m-Hydroxybenzoic	197	0·1	3·3				

The acids mentioned thus comprise eleven aromatic and two aliphatic dicarboxylic acids. It is possible that other, more water-soluble acids have been lost during the industrial preparation. As the material investigated had been extracted from hydrolysed urine, we can say nothing about the form of conjugation of these acids in pregnant-mare's urine.

Let us now consider the biochemical implications of these findings.

(*a*) The methoxylated acids, vanillic, ferulic, and dihydroferulic acids, are probably derived from lignin or similar food substances.

(*b*) The isolation of three unsaturated acids, cinnamic, cumaric, and ferulic acid, is worth notice, as it was believed until then that such acids pass into the urine only after administration of large doses. Fischer and Bielig (*Z. physiol. Chem.*, 1940, **266**, 73) found more than half of a dose of several grams of cinnamic acid excreted in the urine of rabbits, whereas Snapper-Yü and Chiang (*Proc. Soc. Exp. Biol. Med.*, 1940, **44**, 30) found only traces of unchanged acid in human urine, after a dose of 6 g. of cinnamic acid. It seems probable that the cinnamic acid derivatives which we have isolated are formed in the organism as intermediates in the oxidation of saturated acids, according to Dakin's well-known scheme (" Oxidations and Reductions in the Animal Body," London, 1922). If this is true, then cinnamic acid is another metabolic product of phenylalanine, and *p*-cumaric acid of tyrosine.

(*c*) Of the two dicarboxylic acids, which we have isolated, azelaic acid has been found by Müller (*J. Biol. Chem.*, 1937, **119**, 121) in the urine of cows, together with pimelic acid. We have not found the latter in pregnant-mare's urine. Azelaic acid, which Hanson (*Ernährung*, 1941, **6**, 273) considers to be a normal constituent of human urine, may easily be formed by oxidation of oleic, linoleic, and linolenic acid, which all have the grouping $X = CH{\cdot}[CH_2]_7{\cdot}CO_2H$, or also, according to Verkade, Van der Lee, and Van Alphen (*Z. physiol. Chem.*, 1937, **250**, 47), from certain acids considered to be " diacidogenic."

As for the decane-1 : 10-dicarboxylic acid, it has never before been found in Nature. Emmrich and Emmrich-Glaser (*Z. physiol. Chem.*, 1940, **266**, 183) have studied its fate after administration to dogs and humans : 6—7% are excreted unchanged in the urine. It is perhaps formed partly by ω-oxidation of long-chain fatty acids. We wish, however, to discuss another possibility, suggested by a reaction studied by Lapworth and Mottram (*J.*, 1925, **127**, 987) and Green and Hilditch (*J.*, 1937, 764). These authors found that the dihydroxy-acids derived from the natural unsaturated acids (for instance, θκ-dihydroxystearic derived from oleic acid, or λμ-dihydroxybehenic derived from erucic acid) are oxidised by permanganate in a peculiar way which is illustrated below for the last-mentioned acid : the carbon chain is cut into three pieces, by rupture next to the two hydroxyl groups; the middle piece gives oxalic acid. Erucic acid being a rather common constituent of natural oils, this mechanism could account for the isolation of decane-1 : 10-dicarboxylic acid.

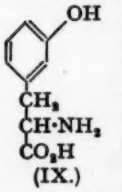
$$CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}[CH_2]_{11}{\cdot}CO_2H \longrightarrow CH_3{\cdot}[CH_2]_7{\cdot}\overset{|}{C}H(OH){\cdot}CH(OH)\overset{|}{-}[CH_2]_{11}{\cdot}CO_2H \longrightarrow$$

$$CH_3{\cdot}[CH_2]_6{\cdot}CO_2H + H_2C_2O_4 + HO_2C{\cdot}[CH_2]_{10}{\cdot}CO_2H$$

(*b*) The case of *m*-hydroxybenzoic acid is still mysterious; this acid has as yet not been isolated from plant material, and its formation by oxidation of a *m*-hydroxylated natural substance remains improbable as long as such a substance has not been found. Dakin and Herter showed long ago (*J. Biol. Chem.*, 1907, **3**, 419) that benzoic acid, treated under certain conditions with hydrogen peroxide, is oxidized to a mixture of *o*-, *m*-, and *p*-hydroxybenzoic acids. This mode of formation *in vivo* seems rather improbable in view of recent work on the

metabolism of aromatic substances, where only *o*- or *p*-hydroxylations have been encountered (Williams, *Biochem. J.*, 1946, **40**, 219; 1947, **41**, 1; Bray, Ryman, and Thorpe, *ibid.*, 1947, **41**, 212).

Another possibility was indicated by a recent paper of Blaschko and Stanley (*ibid.*, 1948, **42**, iii) stating that *m*-tyrosine (IX) is a substrate for some enzymes (dopa-decarboxylase of rat liver, and D-amino-oxidase of pig kidney). We thought that if *m*-tyrosine is a substrate for enzymes it is perhaps a naturally occurring amino-acid, formed in small quantity from phenylalanine at the same time as *p*-tyrosine. If that were so, the presence of *m*-hydroxybenzoic acid in urine would be quite natural. A search for *m*-tyrosine in the mother-liquors of *p*-tyrosine and in the blood and urine of rabbits after injection of phenylalanine has so far been negative.* A last possibility, which should be discussed, is that *m*-hydroxybenzoic acid is formed in the intestine by reductive deamination of 3-hydroxyanthranilic acid, which has recently been shown to be an intermediate in the transformation of tryptophan into nicotinic acid (Albert, Scheer, and Deuel, jun., *J. Biol. Chem.*, 1948, **175**, 479; Heidelberger, Abraham, and Lepkovsky, *ibid.*, 1948, **176**, 1461).


(IX.)

As for the *m*-methoxybenzoic acid isolated from pregnant-mare's urine, nothing can be said concerning its origin; methylations of phenolic hydroxyl groups have not yet been observed in the animal organism. It seems to us that this question deserves to be studied again, because such a methylation could account also for the presence of *p*-methoxyacetophenone and 5-methoxysalicylic acid in the scent gland of the beaver (see Table I).

(3) Wool Fat.

It is not our intention to cover here the whole literature of the chemistry of wool fat, the waxy substance excreted by the sebaceous glands of the sheep on to the wool fibre. The reader may consult our recent review on that subject (Lederer and Velluz, *Ind. Parfumerie*, 1947, **2**, 282). We wish to mention here some results of a chromatographic study of the unsaponifiable portion of wool fat and of an investigation into the biochemistry of the triterpene alcohols of wool fat.

Wool fat is essentially a wax, consisting of esters of branched-chain fatty acids (Weitkamp, *J. Amer. Chem. Soc.*, 1945, **67**, 447) with aliphatic and cyclic alcohols. The most important of these latter are cholesterol and "*iso*cholesterol," which is a mixture of four tetracyclic triterpene alcohols (lanosterol, $C_{30}H_{50}O$, dihydrolanosterol, $C_{30}H_{52}O$, agnosterol, $C_{30}H_{48}O$ and dihydroagnosterol, $C_{30}H_{50}O$) which have been studied in recent years by Ruzicka, Denss, and Jeger (*Helv. Chim. Acta*, 1945, **28**, 759; 1946, **29**, 204) and by Dorée, McGhie, and Kurzer (*J.*, 1947, 1467; *J.*, 1948, 988; *Nature*, 1949, **163**, 140). Lanosterol and agnosterol have the same carbon skeleton (Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368) and their hydroxyl group is at the same carbon atom (2) as in most plant triterpenes (Ruzicka, Montavon, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 818). Their exact structure is as yet unknown, but they are especially interesting as representatives of the small group of animal triterpenes of which only two other members are known—the aliphatic squalene of shark liver oils and the tricyclic ambrein of ambergris (see below).

A chromatographic analysis of the unsaponifiable portion of wool fat led to a separation of six distinct groups, which differed strongly in their optical rotation (Daniel, Lederer, and Velluz, *Bull. Soc. Chim. biol.*, 1945, **27**, 218).

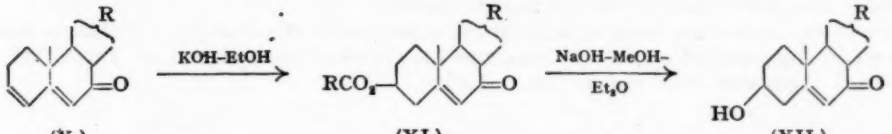
The first fraction, eluted by light petroleum, was optically inactive and consisted of a mixture of low-melting paraffins. Prelog, Ruzicka, and Stein (*Helv. Chim. Acta*, 1843, **26**, 2222) had already isolated paraffins from the unsaponifiables of pig spleen, but had classified them as "impurities," derived from the grease of the machines which had been used in the preparation of their unsaponifiables. On extracting wool in the laboratory without contact with extraneous grease, we prepared a sample of wool fat, the unsaponifiable portion of which had the same percentage of low-melting paraffins as the previously-studied samples of industrial wool fat. This shows that paraffins are genuine constituents of wool fat (and probably also of the unsaponifiables of animal organs), probably derived from the food.

The second fraction obtained by chromatography of the unsaponifiables of wool fat contained a mixture of dextrorotatory keto-steroids.

The third fraction was strongly lævorotatory, owing to the presence of cholesta-3 : 5-dien-7-one

* Unpublished results of Jutisz and Lederer; synthetic *m*-tyrosine was separated by paper chromatography from *p*-tyrosine; no natural extract showed a spot corresponding to *m*-tyrosine.

(X), $[\alpha]_D$ −350°. This substance too had already been isolated from unsaponifiables of vertebrate organs (cf. Prelog, Ruzicka, and Stein, *loc. cit.*) but it had not been possible to decide whether it was natural or an artefact. Mautner and Suida (*Monatsh.*, 1896, **17**, 579) had shown that esters (XI) of 7-ketocholesterol are hydrolysed to cholesta-3 : 5-dien-7-one (X) by alcoholic potash, but that 7-ketocholesterol (XII) is obtained by hydrolysis with ethereal sodium methoxide. We



(X.) (XI.) (XII.)

could easily decide the question as to the origin of cholesta-3 : 5-dien-7-one in wool fat by two parallel hydrolyses of wool fat; one with alcoholic potash, the other with ethereal sodium methoxide. After chromatography, only the former unsaponifiable showed the strongly lævorotatory eluates containing cholesta-3 : 5-dien-7-one. This proves that this latter substance is an artefact and that it arises from the hydrolysis of esters of 7-ketocholesterol, the presence of which is thus indicated in wool fat.

The fourth fraction obtained in the chromatography of the unsaponifiables of wool fat is again dextrorotatory and contains the afore-mentioned triterpene alcohols. The fifth fraction is lævorotatory and contains all the cholesterol. The sixth fraction, finally, is again dextrorotatory; no pure substance could be isolated from it.

Biochemistry of the triterpene alcohols of wool fat. Schulze (*Z. physiol. Chem.*, 1890, **14**, 522) had already stated that "*iso*cholesterol" gives a brown solution with a green fluorescence, in the Liebermann–Burchard reaction. Using this reaction we have developed a colorimetric method for the determination of the wool fat triterpene alcohols in presence of cholesterol. Lanosterol gives a solution with an intense absorption band at 458 mμ., whilst cholesterol and the phytosterols give a green solution with a relatively flat band at 630 mμ. (Schönheimer and Sperry, *J. Biol. Chem.*, 1934, **106**, 745). As all four triterpene alcohols of wool fat give the same colour reaction and with approximately equal intensity, it is possible to estimate the sum of triterpene alcohols by spectrophotometry at 458 mμ. (Lederer and Tchen, *Bull. Soc. Chim. biol.*, 1945, **27**, 419). This colorimetric method can be used to determine the quantity of lanolin (purified wool fat) in pharmaceutical and cosmetic preparations because lanolin contains, as we have found, an average of 11·5% of triterpene alcohols.

In studying, by this method, the "wool fat" extracted from the hair of different animals, we have found that the goat, llama, and camel also excrete small quantities of triterpene alcohols (1·2—2·5% of the "wool fat"), whereas these substances are absent from the fat from the hair of oxen, rabbits, dogs, and humans. The excretion of triterpene alcohols thus seems to be characteristic for the metabolism of certain ruminants.

We have recently examined the unsaponifiable matter of different organs of sheep, to see if the triterpene alcohols participate in the general steroid metabolism or if they are only confined to the skin and the wool (Lederer and Mercier, *Biochim. Biophys. Acta*, 1948, **2**, 91). Liver, kidneys, adrenals, pancreas, brain, pituitary, stomach, and intestine were all devoid of triterpene alcohols (their unsaponifiables containing less than 0·3% of "*iso*cholesterol"). The fat extracted from the skin, on the contrary, contains the same high percentage of triterpene alcohols as the wool fat (15—21% of the unsaponifiable). This shows that the triterpene alcohols do not participate in the steroid metabolism of the sheep, but that they are synthesized by the sebaceous glands and directly excreted on to the wool.

On examining existing evidence concerning the metabolism of the skin (*i.e.*, the sebaceous glands) we think that the peculiar composition of wool fat (branched-chain fatty acids, triterpene alcohols) is an expression of the biosynthetic capacities of the sebaceous glands, which are different from those of the liver. It would be very interesting to see whether acetate is also a precursor for the biosynthesis of the triterpene alcohols as it is for cholesterol (Block, Borek, and Rittenberg, *J. Biol. Chem.*, 1946, **162**, 441). In view of the recent paper of Srere, Chaikoff, and Dauben (*ibid.*, 1948, **176**, 829) in which the adrenal cortical tissue is established as capable also of synthesising cholesterol from acetate, it would not be astonishing if cholesterol, as well as the triterpene alcohols of wool fat, were synthesised by the sebaceous glands (see also Montagna and Noback, *Anat. Rec.*, 1946, **96**, 111).

As the scent glands of the beaver are transformed sebaceous glands, our work on castoreum stresses also the extraordinary metabolic capacities of such glands.

(4) Ambergris.

Ambergris is an intestinal concretion of the sperm whale (*Physeter macrocephalus*); it forms black, brown, or grey pieces weighing sometimes several kilograms. After the death of the sperm whale, ambergris floats on the sea; under the action of air and sun its colour becomes lighter and its odour improves. Extracts of ambergris are still very much appreciated in perfumery because of their odour and fixative power.

Very little was known until recently of the constituents of ambergris. Unlike castoreum, ambergris is composed of only a few characteristic chemical components (see Table III). Let us mention them now more specifically.

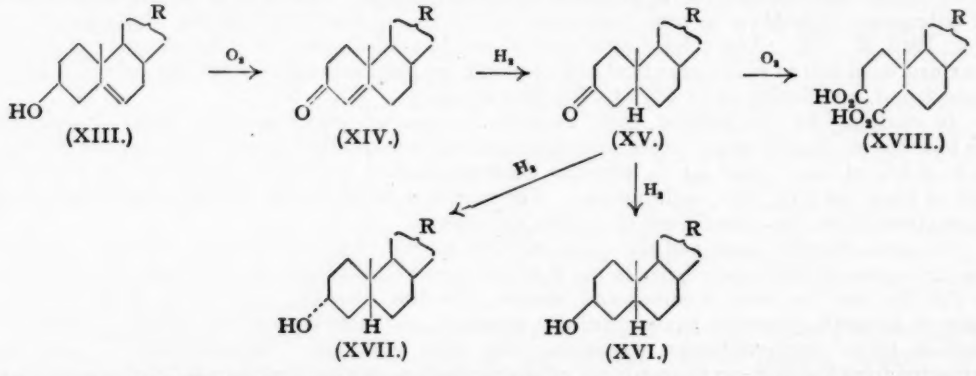
Table III.

Constituents of ambergris.

Ether-insoluble	10—16%	Cholesterol	0·1%
Pristane, $C_{18}H_{38}$	2— 4%	Ketones (of which more than 50% are of coprostane-3-one)	6—8%
Ambrein	25—45%		
*epi*Coprosterol, free and esterified	30—40%	Free acids	5%
Coprosterol	1— 5%	Esterified acids	5—8%

Pristane. In 1943 (*Bull. Soc. Chim. biol.*, 1943, **25**, 1237) we isolated from ambergris a liquid paraffin having the formula $C_{18}H_{38}$ (d^{20} 0·7805, n_D^{20} 1·438). The physical properties of this substance show its identity with pristane, which Tsujimoto and other Japanese authors (*J. Ind. Eng. Chem.*, 1917, **9**, 1098; *J. Soc. Chem. Ind. Japan, Suppl.*, 1937, **40**, 184B; Ueno and Komori, *ibid.*, 1935, **38**, 345B) had isolated from the liver oil of the basking shark (*Cetorhinus maximus*) and from other fish oils. We believe that the pristane of ambergris has its source in the food of the sperm whale. No details are known of the chemical constitution of this substance; as *n*-octadecane melts at 28°, pristane must have a branched structure and, as such as well as because of its animal origin, merits further study.

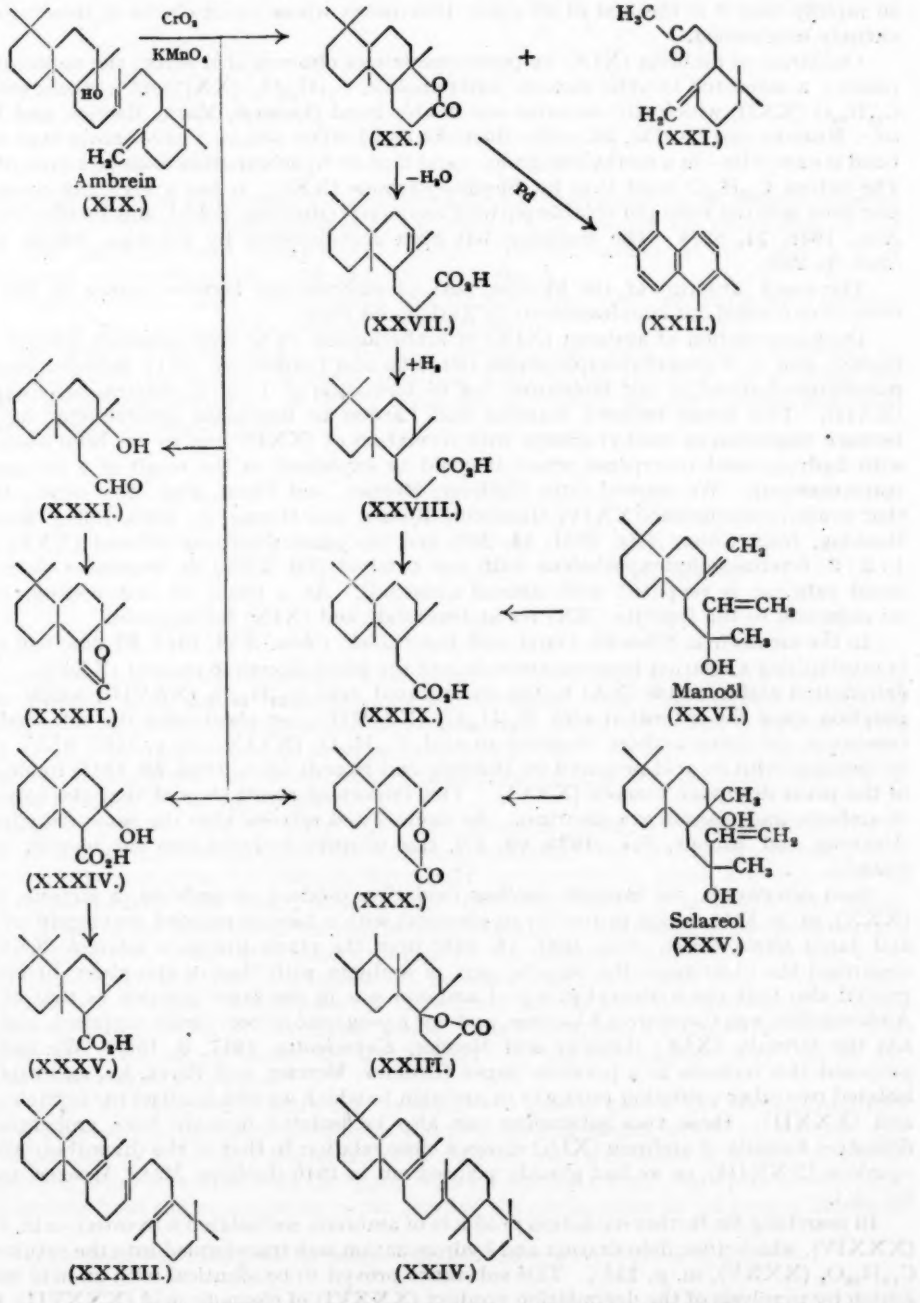
Steroids. We have confirmed the finding of Suzuki (*Jap. J. Med. Sci. Trans.*, 1925, II, **1**, 31) and of Janistyn (*Fette u. Seifen*, 1941, **48**, 501) that ambergris contains coprosterol (XVI) and



*epi*coprosterol (XVII). On treating the unsaponifiable part of ambergris with the reagent *T* of Girard and Sandulesco (*Helv. Chim. Acta*, 1936, **19**, 1095) we have isolated a crystalline keto-steroid which we identified as coprostan-3-one (XV); this is the first time this substance has been isolated from a natural source (Lederer, Marx, Mercier, and Pérot, *Helv. Chim. Acta*, 1946, **29**, 1354). Its presence in ambergris, together with coprosterol and *epi*coprosterol, is a new proof of the exactitude of the theory of Rosenheim and Starling (*Chem. and Ind.*, 1933, **48**, 238) and of Schönheimer, Rittenberg, and Graff (*J. Biol. Chem.*, 1935, **111**, 183) of the formation of coprosterol from cholesterol in the intestine of vertebrates. According to this theory, cholesterol (XIII) is first oxidised to cholest-4-en-3-one (XIV), which is reduced to coprostan-3-one (XV), which is in turn reduced to the two epimers, coprosterol (XVI) and *epi*coprosterol (XVII). Recently Rosenheim and Webster (*Biochem. J.*, 1943, **37**, 513) have isolated cholest-4-en-3-one (XIV) from the fæces of dogs and rats; and Marker, Wittbecker, Wagner, and Turner (*J. Amer. Chem. Soc.*, 1942, **64**, 818) have found *epi*coprosterol (XVII) in the fæces of dogs. Coprostan-3-one (XV) was the last intermediate of this reaction requiring isolation.

The dicarboxylic acid (XVIII), $C_{27}H_{46}O_4$, m. p. 245°, which may be prepared by chromic

acid oxidation of coprostanone was also isolated from ambergris. The recent paper of Turfitt (*Biochem. J.*, 1948, **42**, 376) on the microbial oxidation of steroids indicates that this dicarboxylic acid may be formed in the intestine of the sperm whale by microbial oxidation of coprostanone.



Ambrein. In 1820, Pelletier and Caventou (*J. Pharm.*, 1820, **6**, 49) isolated from ambergris a colourless crystalline substance which they called ambrein. Suzuki (*Jap. J. Med. Sci. Trans.*, 1925, II, **1**, 31) was the first to prepare it in a pure state (m. p. 83°). In 1946, two simultaneous publications established the chemical structure of this substance as being a tricyclic triterpene

alcohol, $C_{30}H_{52}O$, containing one tertiary hydroxyl group and two double bonds (Ruzicka and Lardon, *Helv. Chim. Acta*, 1946, **29**, 912; Lederer, Marx, Mercier, and Pérot, *loc. cit.*). Ambrein is thus the first tricyclic triterpene and a representative of the small group of animal triterpenes (see above). The study of its structure has led to results of general interest and has proceeded so rapidly that it is the first of all cyclic triterpenes whose exact chemical structure has been entirely established.

Oxidation of ambrein (XIX) by permanganate or chromic acid severs the molecule into two pieces: a saturated bicyclic lactone [ambreinolide, $C_{17}H_{28}O_2$, (XX)] and a monocyclic ketone, $C_{13}H_{22}O$ (XXI), which still contains one double bond (Lederer, Marx, Mercier, and Pérot, *loc. cit.*; Ruzicka and Lardon, *loc. cit.*). Ruzicka and Lardon (*loc. cit.*) have shown that the double bond is exocyclic—in a methylene group—and that its hydrogenation leads to tetrahydroionone. The ketone $C_{13}H_{22}O$ must thus be dihydro-γ-ionone (XXI); it has a very fine odour and has also been isolated from the volatile parts of ambergris (Ruzicka, Seidel, and Pfeiffer, *Helv. Chim. Acta*, 1948, **31**, 827). The synthesis has been accomplished by Ruzicka, Büchi, and Jeger (*ibid.*, p. 293).

The exact structure of the bicyclic part of ambrein has become known as the result of researches carried out simultaneously in Zürich and Paris.

Dehydrogenation of ambrein (XIX) or ambreinolide (XX) with selenium gives 1 : 5 : 6-trimethyl- and 1 : 6-dimethyl-naphthalene (Ruzicka and Lardon, *loc. cit.*); dehydrogenation with palladium–charcoal in our laboratory led to formation of 1 : 2 : 5 : 6-tetramethylnaphthalene (XXII). This result induced Ruzicka and Lardon to formulate ambreinolide as (XXIII), because migration of methyl groups with formation of (XXII) had as yet been observed only with hydroxylated triterpenes where it could be explained as the result of a retropinacolinic rearrangement. We showed later (Lederer, Mercier, and Pérot, *Bull. Soc. chim.*, 1947, 345) that *quadricyclo*squalene (XXIV) (Heilbron, Kamm, and Owens, *J.*, 1926, 1630; Ruzicka and Hosking, *Helv. Chim. Acta*, 1931, **14**, 203) and the plant diterpene sclareol (XXV) also give 1 : 2 : 5 : 6-tetramethylnaphthalene with our catalyst [Pd (15%) on vegetable charcoal; the usual catalyst is prepared with animal charcoal]. As a result of this finding, there was no objection to the formulæ (XX) for ambreinolide and (XIX) for ambrein.

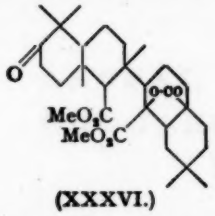
In the meanwhile, Ruzicka, Dürst, and Jeger (*Helv. Chim. Acta*, 1947, **30**, 353) had succeeded in establishing a relation between ambrein and the plant diterpene manoöl (XXVI). They had dehydrated ambreinolide (XX) to the unsaturated acid, $C_{17}H_{26}O_2$ (XXVII), which on hydrogenation gave the saturated acid, $C_{17}H_{28}O_2$ (XXVIII); on shortening the side-chain of this substance, the Swiss authors obtained an acid, $C_{16}H_{26}O_2$ (XXIX), m. p. 126°, which proved to be identical with an acid prepared by Hosking and Brandt (*Ber.*, 1935, **68**, 1311) by degradation of the plant diterpene manoöl (XXVI). This important result showed that the bicyclic parts of ambrein and manoöl are identical. As manoöl and sclareol give the same trihydrochloride (Hosking and Brandt, *Ber.*, 1935, **68**, 37), this identity includes also the bicyclic system of sclareol.

Soon afterwards, we isolated another oxidation product of ambrein, a lactone, $C_{16}H_{26}O_2$ (XXX), m. p. 121°, which proved to be identical with a lactone isolated previously by Ruzicka and Janot (*Helv. Chim. Acta*, 1931, **14**, 645) from the plant diterpene sclareol (XXV). This confirmed the identity of the bicyclic part of ambrein with that of the plant diterpenes and proved also that the hydroxyl group of ambrein was in the same position as that of sclareol. Ambreinolide was therefore a δ-lactone, and not a γ-lactone as previously supposed, and ambrein has the formula (XIX) (Lederer and Mercier, *Experientia*, 1947, **3**, 188). We had already proposed this formula in a previous paper (Lederer, Mercier, and Pérot, *loc. cit.*) after having isolated two other oxidation products of ambrein to which we had ascribed the formulæ (XXXI) and (XXXII); these two substances can also be isolated directly from ambergris.* The definitive formula of ambrein (XIX) shows a close relation to that of the (hypothetical) *tricyclo*squalene (XXXIII), as we had already pointed out in 1946 (Lederer, Marx, Mercier, and Pérot, *loc. cit.*).

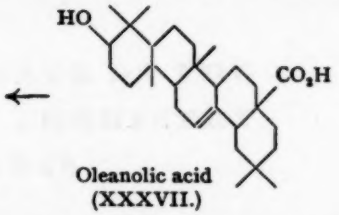
In searching for further oxidation products of ambrein, we isolated a hydroxy-acid, $C_{15}H_{26}O_3$ (XXXIV), which after dehydration and hydrogenation was transformed into the saturated acid, $C_{15}H_{26}O_2$ (XXXV), m. p. 135°. This substance proved to be identical with an acid isolated in Zürich by pyrolysis of the degradation product (XXXVI) of oleanolic acid (XXXVII), the most common pentacyclic triterpene acid derived from β-amyrin (Ruzicka, Gutmann, Jeger, and Lederer, *Helv. Chim. Acta*, 1948, **31**, 1746).

* The hydroxyl group in the formulæ for ambrein and ambreinolide had been until then placed at the carbon atom carrying the side-chain, and not on that carrying the methyl group.

As the bicylic part of ambrein had already been shown to be identical with the corresponding part of sclareol (XXV) and manoöl (XXVI) (see above), and as Jeger, Dürst, and Büchi (*Helv.*



(XXXVI.)

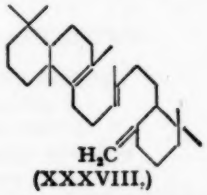


Oleanolic acid
(XXXVII.)

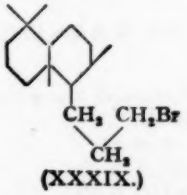
Chim. Acta, 1947, **30**, 1853) had proved the identity of the bicyclic system of the manoöl–sclareol group with that of the tricyclic diterpenes of the abietic acid group,* we thus come to the conclusion that structure and configuration of the bicyclic system of all these groups (plant diterpenes, plant triterpenes, and ambrein) is identical.

Quite recently, Meisels, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1949, **32**, 1075) have isolated the same C_{15} acid from degradation products of α-amyrin.

Dürst. Jeger, and Ruzicka (*ibid.*, p. 46) have recently described a partial synthesis of ambratriene (XXXVIII), the hydrocarbon resulting from the dehydration of ambrein, by condensing the Grignard derivative of the C_{17} bromide (XXXIX), derived from ambreinolide (XIX), with dihydro-γ-ionone (XXI).



(XXXVIII.)



(XXXIX.)

We know nothing about the biogenesis of ambrein; it is a fact that the sperm whale, having teeth, has different food habits from those of other whales. Its food consists mostly of cephalopods, and one of these, *Elledone moschata*, has a scent gland and is said to have a musk-like odour. Squalene could obviously be a precursor of ambrein. We have observed no change in squalene by treating it with dilute hydrochloric acid for a week, under conditions which could prevail in the stomach of the sperm whale.

Porphyrins. Okahara (*Jap. J. Med. Sci., II., Biochem.*, 1927, **1**, 247) has described a porphyrin isolated from ambergris and called ambraporphyrin. We have shown recently that ambraporphyrin is a mixture of protoporphyrin and *meso*porphyrin which are separable by chromatography (Lederer and Tixier, *Compt. rend.*, 1947, **224**, 531). It is known that proto-porphyrin is found in the intestine of vertebrates as a result of hæmorrhages in the intestine and that it is usually partly reduced to *meso*porphyrin by the intestinal bacteria (Zeile and Rau, *Z. physiol. Chem.*, 1937, **250**, 197; Grotepass and Defalque, *ibid.*, 1938, **252**, 155). We suppose that the numerous "beaks" of cephalopods, which are always found in ambergris, provoke hæmorrhages in the intestine of the sperm whale, with subsequent formation of proto- and *meso*-porphyrins. The lesions caused by the "beaks" of the cephalopods may well be the cause of the formation of ambergris.

Perfumers will be interested to learn that probably the greater part of the odorous products of ambergris are oxidation products of ambrein and that the long-lasting smell of ambergris may be partly explained by a constant autoxidation of ambrein with formation of volatile products. This oxidation is perhaps catalyzed by the appreciable amounts of copper contained in ambergris, which are derived from the hæmocyanin of the blood of the cephalopods in the food of the sperm whale.

* This paper definitely fixed the position of the angular methyl group of ambrein.

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